VOLUME 95 • FEBRUARY 1958 • NUMBER 2

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DISEASES OF CHILDREN

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TABLE OF CONTENTS

VOLUME 95 FEBRUARY 1958 NUMBER 2

ORIGINAL ARTICLES

PAGE

A Quantitative Study of the Absorption of Food Iron in Infants and Children
Jeanette Schulz, M.D., Los Angeles, and Nathan J. Smith, M.D., Madison, Wis. 109

Quantitative Study of the Absorption of Iron Salts in Infants and Children
Jeanette Schulz, M.D., Los Angeles, and Nathan J. Smith, M.D., Madison, Wis. 120

A Quantitative Study of the Fate of Recently Absorbed Food Iron
Robert C. Neerhout, M.D., Baltimore; David H. Armstrong, M.D.; Jeanette Schulz, M.D., Los Angeles, and Nathan J. Smith, M.D., Madison, Wis. 126

Enteropathogenic Escherichia Coli Diarrhea
J. J. Quilligan Jr., M.D., and Smith Shadomy, B.A., Los Angeles 134

A Study of the Hearing Level Following Severe Poliomyelitis
Randolph Batson, M.D., and Freeman McConnell, Ph.D., Nashville, Tenn. 139

Prochlorperazine as an Antiemetic in the Severely Retarded Child
H. H. Berman, M.D.; Martin Lazar, M.D., and Ossy Noe, M.D., Staten Island, N. Y. 146

Mammalian Bites of Children
Hugh A. Carithers, M.D., Jacksonville, Fla. 150

Studies in Sickle-Cell Anemia
Henry T. Carrington, M.D.; Angella D. Ferguson, M.D., and Roland B. Scott, M.D., Washington, D. C. 157

Characteristics of Heart Disease Seen in a Case-Finding Program
H. J. Dodge, M.D., M.P.H.; Naomi M. Morris, M.D., and George J. Maresh, M.D., Denver 164

Congenital Aortic Stenosis in Young Children
A. A. Eggink, M.D.; H. A. Ph. Hartog, M.D., and Fred Kuipers, M.D., Amsterdam, Netherlands 170

Prednisone in the Treatment of Allergic Diseases in Children
Samuel J. Levin, M.D., and Philip Adler, M.D., Detroit 178

Excretion of Thiamine and Riboflavin by Children
Genevieve Stearns, Ph.D.; Lucile Adamson, M.S.; J. B. McKinley, M.S.; Theodore Linner, M.S., and P. C. Jeans, M.D., Iowa City 185

Annular Pancreas Producing Duodenal Obstruction in the Newborn
Donald Weatherill, M.D.; Edward G. Forgrave, M.D., and William S. Carpenter, M.D., Detroit 202

PROGRESS IN PEDIATRICS

Acute Pancreatitis in Children
Gunnar B. Stickler, M.D., Rochester, Minn., and Robert H. Yonemoto, M.D., Los Angeles 206

CASE REPORTS

Eosinophilic Granuloma
Holden C. McCraney, M.D., Fort Smith, Ark., and Alfred B. Falk, M.D., Chicago ... 214

CORRESPONDENCE

Premature and Full-Term Infants: A Comparison of Their Maternal Histories
Hilda Knobloch, M.D., Columbus, Ohio 217
Stuart S. Stevenson, M.D., Pittsburgh 218

REGULAR DEPARTMENTS

Abstracts from Current Literature 219
News and Comment 232

A. M. A.
Journal of Diseases of Children

VOLUME 95 FEBRUARY 1958 NUMBER 2

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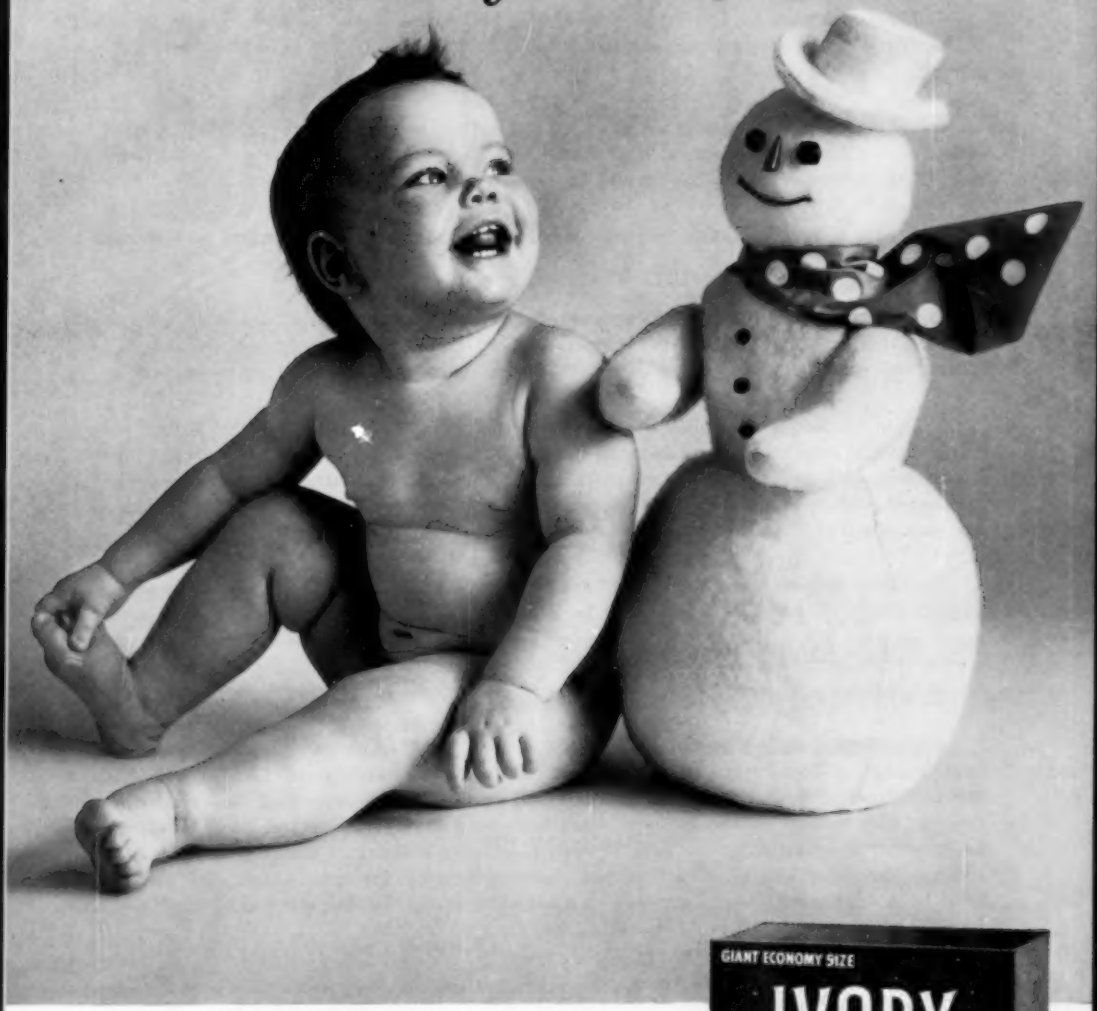

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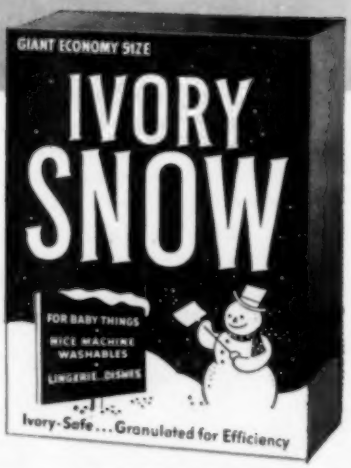

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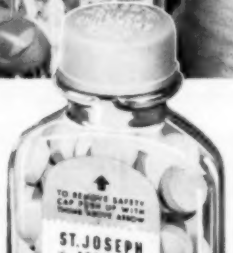

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A Quantitative Study of the Absorption of Food Iron in Infants and Children

JEANETTE SCHULZ, M.D., Los Angeles, and NATHAN J. SMITH, M.D., Madison, Wis.

Iron deficiency is the commonest nutritional deficiency encountered in children. Its incidence in a given area appears to be a fairly accurate indicator of the economic status and the efficiency of preventive medicine in that area. Though other deficiency diseases are decreasing, the incidence of iron deficiency in at least one area in this country has not changed significantly in the past 20 years.[1] Anemia due to iron-deficiency is commonest in infants, aged 6 months to 2 years.[2,3] Though etiologic factors such as low iron stores at birth, blood loss, and intestinal parasitism must be considered, a dietary intake of iron insufficient to satisfy iron requirements during growth is the single most important cause of iron deficiency in infancy. The lower the total body iron content of a given infant the greater his need for exogenous iron for growth.

In order to determine the availability of food iron for hemoglobin production in children, balance studies were conducted on 126 children, with use of radioisotope techniques first described by Dubach and Moore in 1951.[4] These authors found that normal and iron-deficient adults absorb less than 10% of the iron naturally occurring in food.

Earlier studies[5-9] on food iron absorption in children are inconclusive because of the difficulty of quantitative analysis of nonradioactive iron from food and feces and because such unabsorbed iron in the stool cannot be differentiated from iron lost in bile, desquamated intestinal epithelial cells, and blood cells or from contaminating extraneous iron. Other studies utilized iron salts, which are not representative of iron from usual dietary sources.[10,11] In some earlier experiments balance periods were too short to afford accurate information about the quantity of absorbed iron. Occasionally the rise in plasma iron after feeding was used as an indicator of absorption. A failure to demonstrate a postprandial rise in plasma iron is not proof that no iron was absorbed.

In the present study the quantity of radioiron absorbed is considered to be that amount of the ingested iron which did not appear in the feces. The amount of ingested iron absorbed and used for hemoglobin production is that quantity of the administered iron isotope which was present in the circulating red blood cells two weeks after the tagged-iron feeding. Since tracer doses of radioisotopes of natural elements are metabolized in the same manner as the nonradioactive elements,[12] and since the tra-

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Bank of America-Giannini Foundation Research Fellow, Department of Pediatrics, University of California School of Medicine at Los Angeles (Dr. Schulz); Professor of Pediatrics, University of Wisconsin School of Medicine (Dr. Smith).

cer iron was given in a chemical form identical to that of the nonradioactive iron in the feeding, the fate of the administered tracer iron is representative of the fate of the total iron in a feeding.

Methods

1. *Experimental Subjects.*—Normal children 3 months to 15 years of age selected for study were those whose past histories gave no indication of previous anemia, blood loss, or illnesses other than the usual upper respiratory or exanthematous diseases of childhood. In the several weeks prior to and during the experimental period all children described as normal were clinically well. Any child in whom the balance period might have coincided with the incubation period of a subsequent illness was excluded from the list of normal subjects. None of the normal children was hospitalized. Feeding and stool collections were completed in the home, and only those subjects for whom quantitative stool collection was achieved are included in the study. No gross mental or physical handicaps were apparent in this group.

Sick children, with or without anemia, were studied during their stay on the pediatric wards of the U. C. L. A. Medical Center. In some cases of iron-deficiency anemia growth and development were somewhat compromised and inadequate caloric as well as inadequate iron intake was apparent.

2. *Laboratory Evaluation.*—A careful hematologic work-up, with use of standardized techniques, was done on each subject. Hemoglobin, hematocrit, red blood cell count, reticulocyte count, red blood cell indices, and serum iron determinations were done. Any child with any one value beyond the range for normal persons of the same age was excluded from the group designated "normal children." Subjects who were called "iron-deficient" had hemoglobin values of less than 9 gm. per 100 ml. and other laboratory findings compatible with the diagnosis of hypochromic microcytic anemia, hypoferremia, hypercupremia, elevated free erythrocyte protoporphyrin, and a return to normal of all these values when the child was treated adequately with oral ferrous sulfate after the balance studies were completed.

3. *Balance Studies.*—(*a*) Feeding: A single feeding of isotopically-labeled food iron was administered. Foods used in the study were tagged with Fe^{59} * of high specific activity (1μc. to 3μc. per microgram of iron). Half-life of the isotope is 45 days; β mev=0.46; γ mev=1.3. Gamma radiation from triplicate samples of the labeled feedings was measured in a deep-well scintillation counter (NaI crystal), and activity was recorded as counts per minute (cpm). These same samples were retained and used as standards when the radioactivity of fecal and blood samples was determined. Methods used in labeling foods were essentially those described by Dubach and Moore [4,13] and are discussed separately in the following sections. Foods physiologically tagged with Fe^{59} were cow's milk and liver and chicken liver and eggs. The radiation dose of Fe^{59} varied from 1μc. to 2μc. given orally to each child to 2μc. to 18μc. given orally to adults. Occasionally studies were repeated in the same person, with intervals of four months to one year between balance periods. The chemical dose of iron varied with the iron content of the food under consideration.

Feedings were given in the morning after an overnight fast. Water was allowed ad lib. Usual diets were resumed three hours after the test feeding. No vitamins were given on the day of feeding, and laxatives and other medications were withheld during the experiment.

(*b*) Stool Collections: All stools were collected quantitatively until less than 2% of the ingested Fe^{59} appeared in a 24-hour collection. Feces and all extraneous material such as toilet tissue and diaper liners were collected in quart jars in which the conglomerate material was homogenized in an electric blender and wet-ashed by boiling in concentrated H_2SO_4. The suspension was brought to constant volume with H_2SO_4 and sampled volumetrically in triplicate (later duplicate), and γ-radiation from Fe^{59} in the samples was measured in the deep-well counter.

After the fifth day following the isotope feeding feces from infants and small children were invariably free of measurable radioactivity. In older children and adults stool collections were usually completed in seven or eight days, but in some adults longer periods were required. All subjects who developed any gastrointestinal symptoms during the collection period were excluded from the study.

(*c*) Hemoglobin Fe^{59}: In many subjects blood was drawn on the 14th day after the labeled food was given. Fe^{59} utilized for hemoglobin production was determined by measuring the radioactivity of samples of packed red blood cells. Blood specimens were centrifuged to constant volume; plasma and white blood cell layers were removed, and γ-radiation of samples of packed red cells in tubes of known volume were counted as above.

4. *Calculations.*—Absorption: Food Fe^{59} absorbed was considered to be the amount of Fe^{59} in the feeding minus that which appeared in the stool.

$$\frac{\text{cpm of } Fe^{59} \text{ in stool}}{\text{cpm of } Fe^{59} \text{ in feeding}} \times 100 = \% \text{ of food } Fe^{59} \text{ absorbed} \qquad (a)$$

Utilization: The per cent of the administered Fe^{59} utilized for hemoglobin was determined as follows:

* Abbott Laboratories, North Chicago, Ill.

$$\frac{\text{cpm/cc. packed RBC} \times \text{total PCV (cc.)}}{\text{cpm of } Fe^{59} \text{ in feeding}} \times 100 \qquad (b)$$

An arbitrary figure of 70 cc. per kilogram of body weight for blood volume was selected after a review of the literature on blood volume determinations.[14-17] Though this figure may be slightly low for the newborn and adolescent periods, the error is probably no greater than that involved in single determinations based on plasma or red blood cell volumes. Several blood volume determinations using Cr^{51}-tagged red cells were done on infants at the time hemoglobin Fe^{59} was determined. Differential counts of the two isotopes were done spectrophotometrically and with differential shielding in the deep-well counter.[18] Calculated blood volumes in these children were 70 to 75 cc. per kilogram. In view of the error involved and the undesirability of the procedure in normal children, estimated figures are used in most of the calculations of total blood volume in this experiment. Venous hematocrit value was multiplied by 0.87 to give an approximation of total body hematocrit value and also by 0.95 to correct for trapped plasma after centrifugation of the red cells.[16] An example of the calculations in a 30 kg. child with a corrected hematocrit value of 38 is as follows:

30 (kg.) × 70 (cc/kg.) × 0.38 (body Hct. %)
(measured) (estimated) (measured and cal.)
× cpm/cc. packed RBC = cpm of
(measured)
total hemoglobin Fe^{59}

Quantitative urine specimens were collected in three subjects for one week after the isotope feeding. The specimens were concentrated and counted for radioactivity, and, as expected, none was found.

Plasma from the blood specimens drawn for determinations of hemoglobin Fe^{59} two weeks after isotope feedings contained no detectable radioactivity.

Absorption of Iron from Cow's Milk

To determine the availability of iron from cow's milk, balance studies were done utilizing milk tagged in vivo with the isotope Fe^{59}. A lactating cow was repeatedly infused with Fe^{59} in the ferrous form. The isotopically labeled milk obtained was pasteurized and homogenized in the usual way.† Homogenization was important to the experimental procedure for several reasons: (1) Investigation showed a higher percentage of Fe^{59} in cream than in the skim layer of the milk, and (2) market milk is generally homogenized, and iron content during processing is augmented.

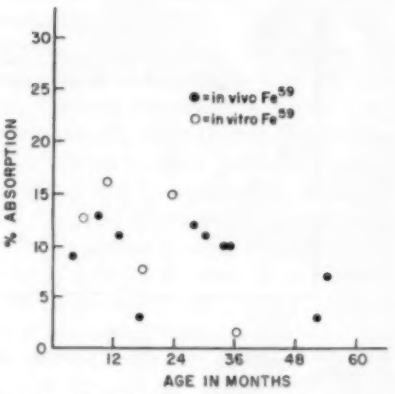

Fig. 1.—Absorption of milk iron in children from birth to 5 years of age.

Six ounces of the milk was fed quantitatively to 10 normal fasting children aged 4 to 52 months. From 3% to 13% of the iron was absorbed (Fig. 1), i. e., 97% to 87% of the isotope appeared in the stool within four days. No radioactivity was detectable in the stool collections on the fifth day in any of the children.

In order to determine the differences, if any, between absorption of naturally occurring milk iron and iron salts added to milk, tracer doses of Fe^{59} as ferrous sulfate were added to 6 oz. of homogenized cow's milk in vitro, and balance studies in five normal fasting children of similar ages revealed absorption of 2% to 17% of the added iron. Total chemical iron content of individual feedings of both the in vivo- and in vitro-labeled milk was the same: 0.1 mg. in the 6 oz. feedings. Radioactive iron of high specific activity added negligible amounts of iron to that already present in the milk. The mean absorption of ferrous iron added to milk (10.6%) was about the same as the absorption of the in vivo-tagged milk iron (9.1%). The absorption of milk iron by four iron-deficient infants, aged 11 to 18 months, was 11% to 24%, with a mean of 16% (Fig. 2).

Larger quantities (600 cc.) of in vivo-labeled cow's milk were fed to normal fast-

† In electrophoresis of milk samples, Fe^{59} migrated in the position of the immune globulins, near, but separated from, casein (Max Kleiber, Ph.D., and Jack R. Luick, Ph.D., Department of Animal Husbandry, University of California, Davis, Calif.).

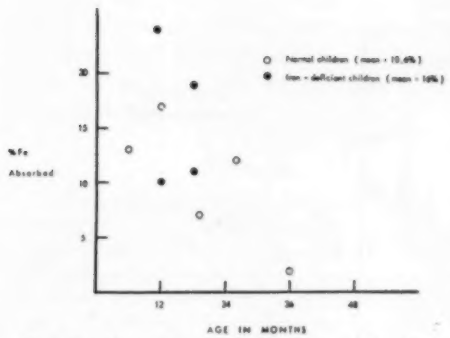

Fig. 2.—Absorption of $Fe^{59}SO_4$ in milk (total iron, 0.09 mg.).

ing adult men. Average absorption of iron in these men was 2.8%. Table 1 shows the recovery of milk Fe^{59} in the stool and blood of the adults and the children from whom blood specimens were obtained two weeks after the milk feeding. At least five times more iron was absorbed by most children than by adults. A consistent finding throughout these studies has been the higher percentages of iron absorption in children in comparison with those reported for adults. The mean per cent of milk iron absorbed and that utilized for hemoglobin formation is about the same. Though small quantities of iron may be absorbed and not utilized for hemoglobin formation within two weeks, gross discrepancies are not apparent between the two sets of determinations. Since the errors in estimation of blood volume alone could account for the deviations from 100% total recovery, absorption figures based on recovery of Fe^{59} incorporated into hemoglobin are not considered more accurate than absorption figures based on recovery of Fe^{59}

TABLE 1.—*Recovery of Fe^{59} Administered in Milk*

Subjects	% of Administered Fe^{59} Recovered		
	in Stools	in Blood	Total
Children			
1	80	17	97
2	90	14	104
3	99	2	101
4	91	7	98
5	80	13	93
Adults			
1	99	2	101
2	98	1	99
3	99	4	103
4	96	3	99
5	98	2	100
6	93	1	94

from feces. Quantitative stool collection is obviously essential for accurate determinations, and many subjects are necessarily dropped from study because of unsuccessful attempts to collect all stool.

The average absorption of iron from cow's milk in the infants and children in this study is much less than that reported by previous investigators using other techniques.[5,6] The statement that infants do not become iron-deficient because of lack of iron in food or because of deficient absorption [6] is not compatible with our figures for absorption. Many infants would have to absorb more iron than is present in milk to avoid not only iron deficiency but also frank iron-depletion anemia.

The slightly less than 3% mean absorption in adults is less than that for children and is of about the same magnitude as absorption of iron from other food sources by adults.[4,19] The greater quantity (i. e., bulk) of milk ingested by adults is probably of little importance relative to the quantity of the infant feedings. Certainly the total iron given (0.4 mg.) was not appreciably greater.

When the cow was killed, the beef liver tagged with Fe^{59} was prepared by mincing the cooked liver, sampling it, and measuring it by weight. Quantitative feeding was attempted, but balance studies were completed in only one normal child, who ate the liver without other food after an overnight fast. Twenty per cent of the liver Fe^{59} was absorbed, and sixteen per cent appeared in the circulating red blood cells in two weeks after the feeding. Total iron content of the liver feeding was not determined, but it was undoubtedly much greater than that of the milk feeding. In this one normal child, assimilation of iron from beef liver was about twice as great as assimilation by any of the subjects given the milk feeding.

Absorption of Fe^{59} from Iron-Supplemented Infant Cereals

Cereal is perhaps introduced earlier and more frequently into infants' diets than any

other solid food. Infant cereals generally available at this time are, for the most part, supplemented with iron, often as sodium iron pyrophosphate. Since the amount of iron added is greatly in excess of that iron naturally found in cereals, the absorption of iron from the supplemented cereals was studied.

Tracer doses of Fe^{59} as sodium iron pyrophosphate, in addition to the usual 50 mg. of iron per 100 gm. of cereal, were added to mixed cereal, oatmeal, and rice cereal by a manufacturer of baby foods in a manner identical to that used in the commercial preparation of the cereals.‡ Total radioactivity of each feeding was measured in the deep-well counter.

For balance studies, 6 gm. portions of cereal were fed with 2 oz. of whole milk to 17 normal fasting children, 3 to 26 months of age. Six grams is a smaller than average feeding of cereal for infants. The iron content of the feeding was 3 mg. (20 mg. of $Na_8Fe_4[P_2O_7]_8 \cdot 6H_2O$), the same as is usually present in like quantities of these supplemented cereals. The tracer dose of Fe^{59} added only negligible amounts of iron to the total iron content.

Figure 3 shows the results of the balance studies with cereals. Absorption ranged from 0 to 25%, with a mean of 12.3%. No significant differences among the three types of cereals are apparent. The higher content of phytate in oatmeal did not lessen the absorption of iron added to that cereal. Sharpe et al.[20] also found that the phytate in rolled oats did not interfere appreciably with iron absorption and suggested that, because oats are fed with milk, calcium binds the phytate, which is then unavailable for the formation of the relatively insoluble iron phytate. The iron content of the cereal feeding was about 30 times that of the feeding used for balance studies with milk alone. In the cereal, iron was present in the ferric form. In the milk, the iron was nondialyzable and probably protein-bound. Because of the differences in chemical form, absorptions in the two experiments are not comparable. However, increasing the total available iron per se did not appear to decrease the efficiency of absorption. Since the mean percentages of iron absorbed in the two experiments are about the same (9% to 12%), the average total amount of iron absorbed from the supplemented cereal feeding was much larger than that from the milk feeding: 0.37 mg. from cereal compared with 0.009 mg. from milk.

‡ Gerber Baby Foods, Oakland, Calif.

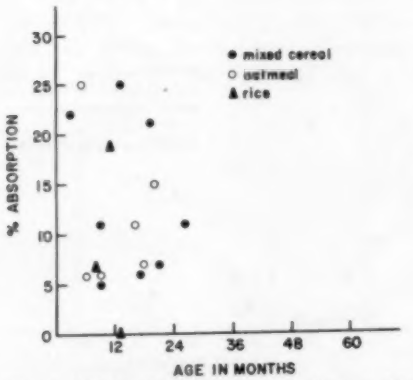

Fig. 3.—Absorption of Fe^{59} from iron-enriched infant cereals (total iron in feeding, 3 mg.).

Absorption of Iron from Eggs

Perhaps the simplest and most efficient physiological tagging of food with radioiron is accomplished by labeling chicken liver and eggs.

The method used in this experiment is about the same as that described by Moore and Dubach in 1951:[4] Fe^{59} of high specific activity was injected intravenously into laying hens in small doses three times a week. Eggs with sufficient radioactivity for balance studies were obtained within one week after the first injection. Each egg contained 1μc. to 2μc. of Fe^{59} and a total of about 1.2 mg. of nondialyzable iron. The eggs were beaten, sampled, measured, scrambled with water, and fed to normal fasting children.

In five children, 8 to 45 months of age, the egg was fed alone and no other food was given for the next three hours. An average of 11% of the iron was absorbed.

Because of the availability of eggs labeled physiologically with iron, balance studies with the eggs were done in a large number of children in an attempt to determine the differences, if any, in iron absorption in children of different ages. Moore and Dubach showed that normal male adults absorbed from 1.1% to 8.1% of iron from

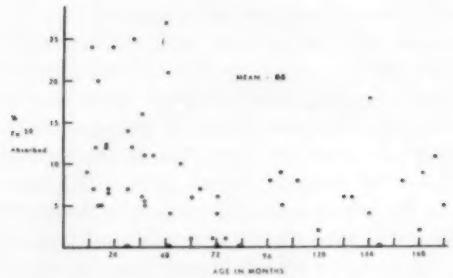

Fig. 4.—Absorption of egg iron in 52 normal children.

eggs, with a mean of 3.8%. In 52 normal fasting children, 1 to 15 years of age, absorption of egg iron was higher, with a mean of 8.6% and a range of 0 to 27%. The results of the individual balance studies are presented in Figure 4. The tagged egg was fed quantitatively to these children after an overnight fast and with a representative breakfast small enough to insure ingestion by all experimental subjects: 2 oz. of orange juice, one slice of white toast with butter, and 2 oz. of milk. Average per cent of iron absorbed was slightly less than when egg alone was fed, but the small number of subjects in the latter group does not lend significance to the observed difference. The difference does, however, tend to reaffirm the findings of Sharpe et al., who observed that iron absorption shows an inverse relationship to the bulk of the feeding, regardless of other factors involved.[20]

Figure 5 shows the results of feeding iron and egg in different combinations under the same fasting conditions. The first group of five children had the naturally occurring (in vivo-labeled) egg Fe^{59}, and these five children were mentioned above (mean amount of iron absorbed, 11%). The second group, of three children, was given a tracer dose of Fe^{59} as ferrous sulfate added in vitro to a nonradioactive scrambled egg. Twelve per cent of the Fe^{59} was absorbed by these subjects. In the third group, in vivo-bound Fe^{59} in chicken liver was fed with a scrambled egg to three children. An average of 8% of the liver Fe^{59} was absorbed under these circumstances. Unfortunately,§ chicken liver Fe^{59} could not be fed alone because quantitative ingestion in small children would have necessitated gavage feeding. The liver was therefore fed with the scrambled egg for comparative purposes. Though significant differences in absorption are not apparent in the small number of balance studies in the three groups, it is interesting that the absorption of the Fe^{59} from chicken liver in three children is less than egg Fe^{59} fed under like conditions. It is also about one-third the amount of iron absorbed from the beef liver which was given alone to one child. Moore et al. found absorption of 0.2% and 33% of chicken liver Fe^{59} and 4% to 9% of chicken muscle Fe^{59} when these foods were fed alone to fasting normal adults.[4] The exact circumstances governing the sporadic occurrence of high percentage of iron assimilation from food by apparently normal persons are not evident from these studies.

The fourth group of children, aged 5 to 32 months, received in vivo-labeled Fe^{59} raw egg in 6 oz. of milk. Seven per cent of the iron was absorbed, with a range of zero to eleven per cent. This quantity of milk added to egg appeared to decrease the efficiency of egg iron absorption. These children served as controls for subjects of the same age with iron-deficiency anemia. The latter

§ Chodos et al.[19] have shown that eggs exert an inhibitory effect on iron absorption.

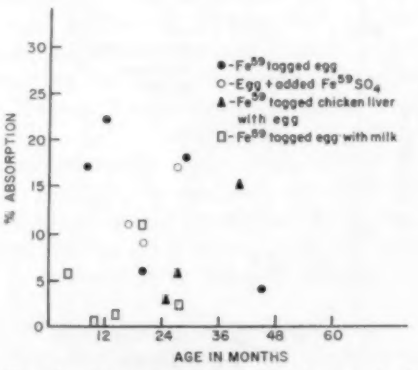

Fig. 5.—Absorption of various forms of Fe^{59} with egg.

group refused scrambled egg feeding and were therefore fed the egg-milk mixture quantitatively. Figure 6 shows the results of balance studies in the iron-deficient group of infants. Ten to twenty-two per cent of the iron was absorbed. Five to eighteen per cent appeared in the circulating red cell mass. The amount of naturally occurring egg iron assimilated by the anemic infants is about three times greater than that utilized by normal infants. This finding is in direct contrast to that of Moore et al., who observed that iron-deficient adults did not absorb more iron from egg than did normal adults.[4] If the differences are real, some particular component of the total body iron in anemic adults may be quantitatively normal but unavailable for hemoglobin production—so-called "inviolable iron." However, in the anemic infant who has probably been iron-deficient since early in life, the same component may be relatively depleted, owing to lack of iron during growth, and so be influential in food-iron absorption mechanisms. Since adults and children with iron-deficiency anemia absorb more iron salts than do normal subjects,[19,21,22] the postulated physiological influence on absorption is obviously not operable when large doses of ionic iron are administered.

Table 2 shows the rather constant discrepancy noted between the amount of egg Fe^{59} absorbed and that found in the circulating red cells. For this reason, studies were undertaken to determine the amount of tissue Fe^{59} present in dogs after feeding of isotopically labeled food iron. These studies, to be reported later, indicate that a very small amount of absorbed food Fe^{59} is utilized for purposes other than immediate erythropoiesis. However, failure to recover more than 1% to 2% of the administered Fe^{59} is probably due to the experimental error and the estimations of total hemoglobin mass.

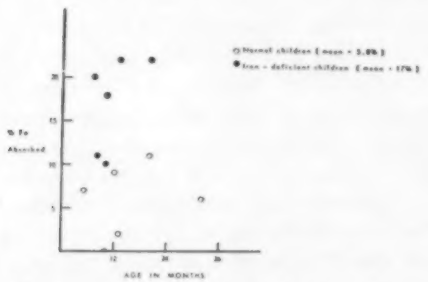

Fig. 6.—Absorption of egg iron with milk.

TABLE 2.—*Relationship Between Egg Fe^{59} Absorbed and That Subsequently Found in Red Blood Cells* *

Normal Subjects						Iron-Deficient Subjects		
A	B	C	A	B	C	A	B	C
20	17	−3	0	0	0	22	18	− 4
10	4	−6	1	2	+ 1	11	7	− 4
1	2	+1	2	1	− 1	22	14	− 8
9	7	−2	4	3	− 1	18	8	−10
4	1	−3	1	4	+ 3	10	5	− 5
20	13	−7	2	2	0	24	14	−10
16	11	−5	7	1	− 6	11	5	− 6
11	5	−6	6	5	− 1	19	12	− 7
19	12	−7	21	11	−10			
4	4	0	2	1	− 1	Mean = −7		
3	4	+1	6	1	− 5			
3	3	0	6	4	− 2			
4	3	−1	0	0	0			
6	1	−5	8	0	− 8			
0	1	+1	0	1	+ 1			
10	5	−5	6	9	+ 3			
0	4	+4	0	0	0			
4	2	−2	0	2	+ 2			
4	2	−2	7	1	− 6			
0	1	+1	6	5	− 1			
		Mean = −2						

* A = % Fe^{59} absorbed (not found in feces); B = % Fe^{59} in circulating red blood cells two weeks after Fe^{59} ingestion; C = difference between A and B.

Because of the large number of normal children who ate the tagged egg with breakfast, this group was analyzed statistically. The data reveal that many apparently healthy children absorb considerably more than 10% of food iron. Children less than 3 years of age absorbed more egg iron than did children 3 to 10 years of age. The difference between these two age groups is statistically significant.‖ Figure 7 illustrates the first- and third-degree regression of iron absorption in relation to age. Although the third- degree curve rises in the older age groups, our data do not permit conclusions on the direction of the curve during adolescence nor on differences which may exist between the requirements of males and females.

The low percentage of iron assimilation by 5- to 8-year-old children has been a recurrent finding in these balance studies.

‖ Significance: t=2.35 at 95% confidence level.

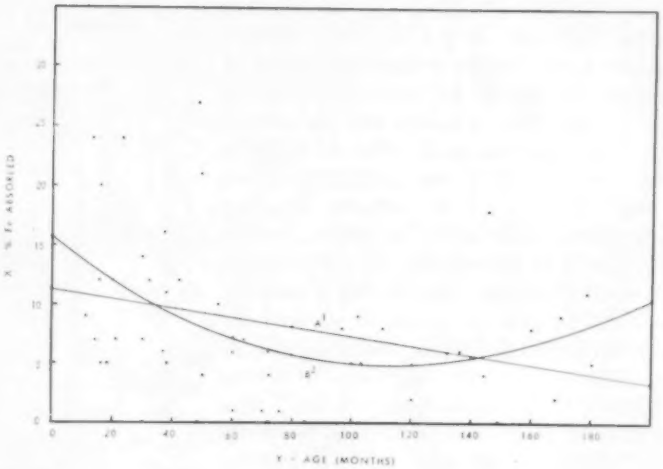

Fig. 7.—First- and third-degree regression of absorption of egg iron in relation to age. Regression equations for *A* and *B*: (1) straight-line first-degree regression, $X=11.24-0.03903Y$; (2) third-degree regression curve, $X=15.63-0.2015Y+0.1045\times10^{-2}Y^2-0.8671\times10^{-4}Y^3$.

Karlberg and Lind found that increases in total hemoglobin per kilogram of body weight are inversely proportional to increase in body weight per kilogram per year. Blood volumes and total hemoglobin per kilogram were especially low at 6 and 7 years, during the second acceleration in growth, and when the rate of growth slowed down blood values again increased. It is interesting to speculate that food iron absorption is perhaps related to their findings.

Figure 8 is a summary of 98 of the balance studies with food iron. It is shown to reaffirm the conclusion that normal children can be expected to absorb about 10% of iron from many foods.

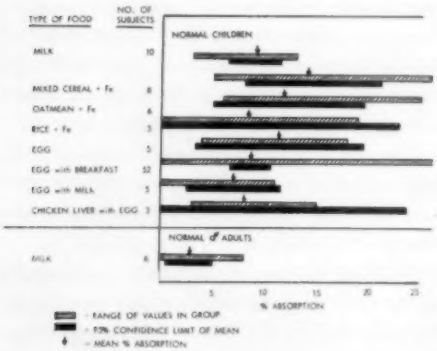

Fig. 8.—Absorption of food iron.

Comment

In the first two years of life the iron requirement of a given infant is the difference between the total body iron present at birth and that needed for hemoglobin production and growth. Any blood loss augments this requirement. Physiological losses (hair, nails, desquamation, etc.) are too minute to be of consequence in this discussion.[24] Since infants are born with varying complements of body iron and subsequently grow at different rates, iron demands may show tremendous variations. It has been estimated that one "normal" infant's need for exogenous iron may exceed that of another by 300%.[23]

If we select a hypothetical infant who at birth weighed 3.5 kg. and had a blood volume of 85 cc. per kilogram and a hemoglobin value of 17 gm/100 ml., the total amount of iron in hemoglobin would be 173 mg. (3.4 mg. Fe per gram of hemoglobin). Estimates of additional body iron are listed in Table 3.[25-28] Storage iron is approximately 20% of total body iron in normal subjects. Tissue iron (myoglobin, enzymes, etc.) is estimated to be 6 mg. per kilogram. The selected infant would have a calculated total body iron value of 229 mg. Assuming that growth proceeded normally, the increments in iron needed in the first 18 months

TABLE 3.—*Calculated Fe Content of a Selected Normal Infant*

Age, Mo.	Body Weight, Kg.	Hemoglobin Fe, Mg.	Storage Fe, Mg.	Tissue Fe, Mg.	Total Fe, Mg.	"Normal" Demand, Mg.
Birth	3.5	173	35	21	229	--
6	8.0	228	23	48	299	70
12	10.0	306	15	60	381	82
18	11.5	350	17	69	436	55

of life are shown. Obviously, "normal" infants' iron requirements might be much greater or less than these, depending on the iron content at birth, the rate of growth, etc.

Table 4 shows the amount of iron our hypothetical normal infant might consume if offered an optimal diet of milk, cereals (iron-supplemented), pureed meats, vegetables and fruit, and egg yolk. Daily intake of iron is approximated from the iron content of the foods [29,30] and the optimal amounts taken by normal infants. The variety and quantity of foods used in these calculations are probably superior to those eaten by most children. If 10% of the iron from these foods is absorbed, it becomes apparent, in our hypothetical infant, that the iron requirements of the first 18 months of life can be satisfactorily met by dietary iron alone if an average of 4 to 5 mg. of food iron is ingested daily after three months of age. However, if an infant is born with less iron or suffers any blood loss even this most optimal of diets may not satisfy his augmented iron demand. Premature infants, for example, could not be expected to absorb sufficient food iron to meet the requirements of growth and increase in hemoglobin mass.

Some correlation was noted in individual normal children between the hematologic values and the per cent of iron absorbed from the test feeding. The regression coefficient (r) of age related to iron absorption is -0.2892; of hemoglobin to iron absorption, -0.1545, and of serum iron to iron absorption, -0.2430; i. e., food-iron absorption is more closely related to either age or serum iron values than to hemoglobin levels in this group of children. No correlation existed between mean corpuscular volume or mean corpuscular hemoglobin and iron absorption. A slight relationship to reticulocyte count or mean corpuscular hemoglobin concentration was found. If, however, relationship of food-iron absorption (x) to combinations of values was calculated by use of the following formula [35]:

$$X=25.67-0.0309\ Y-0.6863\ H-0.0624\ S$$

where

Y=age of child

H=hemoglobin (grams/100 ml.)

S=serum iron (micrograms/100 ml.),

higher regression coefficients were found:

$r_{x.HS}=0.3575$

$r_{x.YS}=0.3520$

$r_{x.YH}=0.2933$

$r_{x.YHS}=0.3585$

Thus it is apparent that in the group of normal children reported here the absorption of food iron is more closely related to age and serum iron levels than to hemoglobin values or red cell indices.¶ Iron-depleted anemic children absorb and utilize much larger amounts of iron, and the differences in comparison to normal controls

¶ It is also apparent that knowledge concerning more than 50% of the factors governing the absorption of iron from a single test feeding such as was given in this experiment is not available from the experimental data.

TABLE 4.—*Calculated Dietary Fe Intake from an Optimal Diet, Birth to Eighteen Months*

Age, Mo.	Fe, Mg.							
	Milk	Infant Cereal	Egg	Meat	Vegetable	Fruit	Total	"Normal" Demand
0–6	78	810	72	60	45	90	1,135	70
6–12	90	1,080	216	360	180	180	2,106	82
12–18	67	90	216	360	200	400	1,333	55

in this study are statistically significant (t-values between the groups are 3.64 and 4.01 at the 95% confidence levels).

Since the average figures for iron absorption in children are higher than those for adults and "normal" hematologic values in young children are indicative of relative iron deficiency when compared with adult values,[23,31] it would be most informative to have precise data on a large population of "normal" infants given more-than-adequate supplemental iron during infancy. If the per cent of food iron absorbed is a reflection of low body iron, one would expect the absorption in such a supplemented group to approximate that of adults. Sturgeon and others have shown that such is accompanied by significant rises in hemoglobin levels in infants.[23,33,34]

Many other factors influence iron absorption. Egg iron balance studies were, advertently and inadvertently, conducted on several children with a variety of illnesses: chickenpox, otitis media, respiratory tract infection, and leukemia. No significant differences in iron absorption were evident. We have recovered 93% to 100% of administered Fe^{59} from the stool of iron-depleted infants (i. e., those with severe iron-deficiency anemia) who developed diarrhea after the test feeding. That such infants did not have a defect in the iron-absorption mechanism was evident when a prompt hematologic response to dietary iron was noted after the diarrhea had abated. To date, we have not encountered any children in whom impairment of the iron-absorption mechanism was demonstrable. One such case, a 7-year-old girl studied by Zetterstrom and Delava, is adequately documented, and in this child a slower than normal utilization of intravenously administered iron for erythropoiesis was also noted.[32] Lack of hematologic response, the basis for many cases reported in the literature, is not adequate evidence of inability to absorb oral iron.

Summary

Balance studies were conducted on 126 children to determine the amount of food iron absorbed and that utilized for hemoglobin production. Normal children absorbed an average of about 10% of the naturally occurring iron in milk, eggs, and chicken liver and the iron supplements added to commercially prepared infants' cereals.

Iron-deficient children absorbed two to three times as much food iron as did normal children.

Normal children absorbed more iron from milk than did normal male adults.

The mean absorption of iron from eggs was higher in younger children than in older children.

A relationship between hematologic values and serum iron and food-iron absorption was demonstrable.

Dietary iron can satisfy the iron requirements of selected normal infants on an optimal diet, but the selected infants are probably not representative of a large segment of the population.

Doris Daniels, Sally Lovett, and Mrs. Robert Schick, of the Department of Pediatrics, University of California School of Medicine at Los Angeles, gave technical assistance.

University Hospitals, 1300 University Ave. (6) (Dr. Smith).

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Quantitative Study of the Absorption of Iron Salts in Infants and Children

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In a previous paper we reported that normal children absorb approximately 10% of iron present in milk, eggs, chicken liver, and iron-supplemented infant cereals. It was observed that children with iron-deficiency anemia absorb food iron more efficiently than do normal children.[1] Since iron supplementation of many infants' diets may be desirable, iron balance studies utilizing radioactive isotopes of iron have been continued to include the absorption of iron salts by normal and anemic children. Other investigators[2-6] using these techniques have shown that in normal and iron-deficient adults ionic iron is more readily absorbed than is food iron and that iron in the ferrous form is absorbed better than ferric iron.[2-6] Similar studies reported to date in children are limited. The work of Darby and his co-workers revealed that children 7 to 10 years of age absorb a greater percentage of a test dose of ferrous iron than do the above-mentioned normal adults. Iron absorption in the children correlated with the estimated yearly increments in body iron during growth.[7] Oettinger et al. demonstrated the ability of premature and full-term newborn infants to absorb and utilize iron in the ferrous state.[8] The present study was undertaken to determine the influence of certain liquids and the size of the iron dose on the absorption of iron salts in normal and anemic infants and children. A ferrous salt was selected because of the published reports that bivalent salts are better assimilated than trivalent ones.[11-14]

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Methods

Balance-study procedures utilizing Fe^{59} as ferrous sulfate for the test feeding are essentially the same as those previously published.[1] The Fe^{59} not found in quantitative stool collections was assumed to have been absorbed. Fe^{59} present in the circulating red blood cell mass two weeks after the test feeding represents the amount of the test dose of Fe^{59} utilized for erythropoiesis. Since the Fe^{59} present in hemoglobin was consistently lower (0 to 4%) than the amount of Fe^{59} not found in the feces, hemoglobin-Fe^{59} figures in this study are not considered representative of the total amount of Fe^{59} absorbed.

Tracer doses of Fe^{59} sulfate used in the experiments were given in a commonly used pharmaceutical preparation* in addition to the nonradioactive $FeSO_4$ in the same preparation. One cubic centimeter of this mixture contains 25.0 mg. of iron. When a single test dose was given, it was administered one to two hours before lunch and at least two hours after the ingestion of other food (breakfast). The four divided test doses were given one hour before each meal and three hours after the evening meal. Children on the twice-daily test schedule received iron one hour before the noon and evening meals. Normal subjects were healthy children, aged 9 months to 5 years, whose hemoglobin, red blood cell indices, and serum iron were within the normal range for age. Current family and past histories were negative for serious illnesses or hematologic disorders. Dietary intake of these children was considered adequate. Balance studies were completed in the home, and usual feeding regimens were not altered. Children with iron-deficiency anemia were studied during their stay on the pediatric wards of the U. C. L. A. Medical Center. Diagnostic features in these patients were typical: hypochromic microcytic anemia, hypoferremia, hypercupremia, and elevated

* Fer-in-Sol, Mead Johnson & Company, Evansville, Ind.

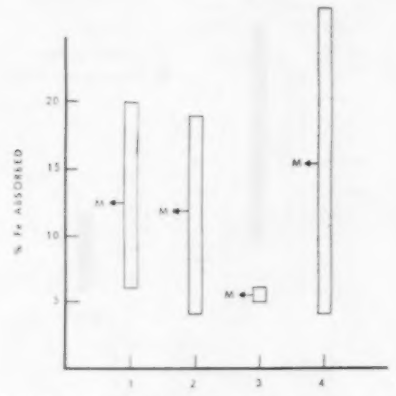

Fig. 1.—Absorption of $FeSO_4$ given two hours before meals to normal children. Group 1: 0.6 cc. q.i.d. (4×12 mg. Fe); Group 2: 1.2 cc. b.i.d. (2×30 mg. Fe); Group 3: 2.4 cc. o.d. (60 mg. Fe); Group 4: 1.2 cc. o.d. (30 mg. Fe). Bar shows range in six children; *M*, mean. There were only two children in Group 4.

free erythrocyte protoporphyrin. All responded well to therapy with ferrous sulfate after the balance studies were completed.

Results

Since the incidence of most severe iron-deficiency in pediatric patients is highest in the 6-month-old to 2-year-old group,[9,10] doses of elemental iron usually given to infants were used in the balance experiments. The first three groups of children received a total of 60.0 mg. of Fe (2.4 cc. of the test solution). The tracer doses of radioactive Fe^{59} did not add significant amounts of elemental iron to that usually present in the preparation used. Figure 1 shows the results of the balance studies in four groups of children. Groups 1, 2, and 4 were composed of six children each, and ages in each group ranged from 9 to 12 months to 4 or 5 years. No significant differences in the amount of iron absorbed (means, 12.7% and 12%) were demonstrated between Groups 1 and 2, i. e., whether the same total daily dose of $FeSO_4$ was given in four or two daily doses. Group 3 furnishes good evidence that 1.2 cc. of the test preparation is the maximum amount of this medication tolerated well by normal children. Of the six children in this group given 2.4 cc. of Fer-in-Sol (60.0 mg. Fe) in a single dose, balance studies were completed in only two children, aged 28 months and 5 years, respectively, and only 6% and 5%, respectively, of the iron was absorbed. Two of the remaining children refused to finish the test feeding, and the other two took it well but vomited a short time later. The fourth group of six children was given a single dose of 1.2 cc. of the ferrous sulfate solution to determine if a single dose was better absorbed than two such doses in one day. More iron was absorbed from the single dose (4% to 27%), but the mean for the group (15.5%) was only slightly higher. The one child who absorbed 27% of the iron was 9 months of age, and 25% of the administered iron was used for erythropoiesis within the two-week period following the test feeding. Hematologic values in this infant were at low normal levels for his age: hemoglobin, 10.5 gm/100 ml.; mean corpuscular volume, 71 cu.μ; mean corpuscular hemoglobin, 23$\mu\mu$g.; serum iron, 64μg/100 ml. These values and the per cent of iron absorbed are perhaps a reflection of the relative iron deficiency in this apparently normal infant. Since a single

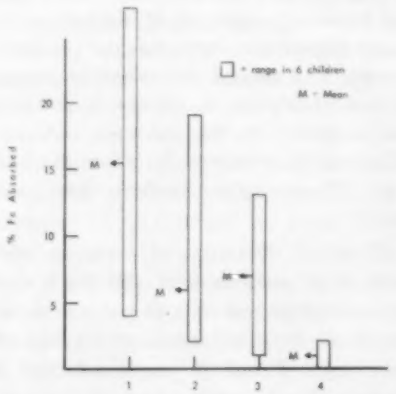

Fig. 2.—Absorption of $FeSO_4$ in normal fasting children. Group 1: 30 mg. Fe alone; Group 2: 30 mg. Fe in 180 cc. milk; Group 3: 30 mg. Fe in 100 cc. orange juice containing 42 mg. added ascorbic acid; Group 4: 30 mg. Fe in 180 cc. milk plus 50 mg. ascorbic acid. Group 4 contained only two subjects.

dose of 30.0 mg. of iron was only slightly more efficiently absorbed than 30.0 mg. of iron given twice a day, the total amount of iron absorbed in a day is much greater when several doses of this magnitude are administered.

Figure 2 compares the quantity of iron absorbed by children given 30 mg. of Fe^{++} with the absorption when the same amount was given with milk or orange juice. The first group of six children is the same as Group 4 in Figure 1 and is included here for comparison. It is evident that 180 cc. (6 oz.) of milk exerts an inhibitory influence on the absorption of the ferrous Fe^{59}, but it seems that any increase in the volume of the test feeding has a like effect. It is unlikely that orange juice would exert any effect other than perhaps some increase in the efficiency of iron absorption. However, in the third group of six children, aged 12 months to 5 years, no such effect was observed. Only 3% to 10% of the Fe^{59} fed to these children appeared in the circulating red cell mass. No gross differences in economic status, nutrition, or hematologic values were found in these normal children when they were compared with the other test subjects. Ascorbic acid content of samples of the fresh orange juice was determined [27] before and after the feeding, and an average value of 42 mg/100 ml. was found. Moore has shown that the quantity of ascorbic acid needed to produce an increase in iron absorption is greatly in excess of that available in the amounts of orange juice usually consumed by infants and children. These studies reaffirm this conclusion.[17]

When an attempt was made to add a solution of ascorbic acid (50 mg.) to the ferrous sulfate and milk to test iron absorption from this combination, only two children, aged 2 and 3 years, tolerated the feeding. The remaining four children either refused to finish the feeding or vomited it later. A purplish-black precipitate formed in the mixture, and the taste was extremely metallic (? elemental Fe). It was obvious

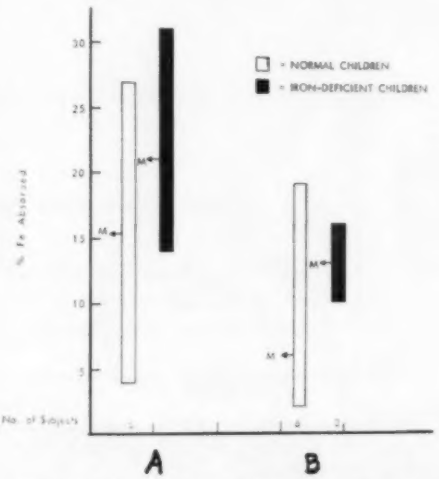

Fig. 3.—Absorption of $FeSO_4$ in iron-deficient children compared with normal children. *A*, 30 mg. $FeSO_4$ alone; *B*, 30 mg. $FeSO_4$ in 180 cc. milk.

that the above combination of ingredients was a most unpalatable mixture, which stained teeth and mouth black and resulted in nausea and vomiting in three very cooperative children. Figure 2 (Group 4) shows that very little of the Fe^{59} from this mixture was absorbed by the two children whose balance studies were completed.

Figure 3 shows that children with iron-deficiency anemia as well as normal children absorb less of a therapeutic dose of $FeSO_4$ given with milk than they do when the iron salt is given alone. When the tagged ferrous sulfate was given alone, a proportionately greater quantity of the iron was also incorporated into hemoglobin by the anemic subjects (10% to 27%). The differences between the absorption of iron, whether it be naturally occurring food iron [1] or iron salts, by normal children and children with iron-deficiency anemia are statistically significant.

Repeated balance studies with ferrous sulfate were conducted on some of the subjects in whom food-iron absorption had been determined earlier.[1] The Table illustrates the results of the two balance studies in each subject. Because of the small number of subjects, the variations in age, type, and

Repeat Balance Studies in Normal Subjects

	Age, Mo.	Feeding	Fe in Feeding, Mg.	% Fe[59] Absorbed
Children				
1	8	Egg	1.2	17
	13	Milk	0.09	11
2	29	Egg	1.2	17
	34	Milk	0.09	11
3	45	Egg	1.2	4
	50	Milk	0.09	7
4	16	Egg	1.2	20
	28	$FeSO_4$ + water	45.0	7
5	6	Cereal (Fe)	3.0	6
	18	$FeSO_4$ + milk	24.0	19
6	18	Cereal (Fe)	3.0	6
	30	$FeSO_4$ + milk	24.0	2
7	17	Cereal (Fe)	3.0	6
	29	$FeSO_4$ + water	24.0	13
Adult males (aged 23–25 yr.)				
1		Egg	1.2	2
		$FeSO_4$	100.0	4
2		Egg	1.2	4
		Fe pyrophosphate	300.0	1
3		Egg	1.2	4
		$FeSO_4$	100.0	2

quantity of iron administered and the bulk of the feedings, no conclusions can be made about this group of experimental subjects. Some children absorbed iron salts better than food iron from a single test feeding. Some absorbed more iron at an earlier age than several months later. Other studies in adults have shown that they can be expected to absorb iron salts more efficiently than iron from food.[5,15] The normal male adults used for repeated control studies in our laboratory did not absorb more iron salts than naturally occurring egg iron when each was given after an overnight fast. However, the total doses of iron were not comparable.

Comment

Adequate treatment of infants and children with iron-deficiency anemia depends upon the quantity and condition of iron absorption. In optimal circumstances, about one-sixth of a 30 mg. dose of ferrous sulfate may be absorbed. If three such doses are given daily, about 15 mg. of iron might be absorbed daily. Since in actual practice conditions for absorption are often less than ideal and infants are frequently not given the prescribed doses, more than the calculated amount of iron needed will probably have to be prescribed before therapy is adequate.

If we arbitrarily choose a milk-fed 18-month-old iron-deficient infant who weighs 10 kg., has a blood volume of 700 cc., and has a hemoglobin value of 6 gm. per 100 ml., his total hemoglobin iron is about 143 mg. (3.4 mg. Fe per gram of hemoglobin). If nonhemoglobin iron totals 60 mg. (6 mg. per kilogram, perhaps too high in this instance), the infant's total body iron is about 200 mg., since storage iron is probably depleted. This child may have been born with a deficit of 100 mg. of body iron, or he may have lost it by hemorrhage peri- or postnatally. The total body iron content of some newborn infants has been shown to be about 80 mg. per kilogram.[16] The iron requirements in the first 18 months of life have been estimated to be about 200 mg.[1,17] Earlier studies with milk iron and the present investigation make it unlikely that more than about 16% of the iron in milk is absorbed, even by the iron-depleted infant.[12] Our hypothetical infant would therefore have absorbed only about 40 mg. of iron from milk, leaving a total body deficit of an estimated 240 mg. of iron to be supplied from exogenous sources. As mentioned above, 12 mg. of ferrous iron might be absorbed daily. Theoretically, this infant's iron deficiency could be corrected in 20 days by giving a total daily dose of 72 mg. of iron in three or four divided doses. For the reasons alluded to previously, therapeutic doses of this magnitude would necessarily be required for much longer than 20 days to achieve the desired therapeutic result. We have frequently seen relapses of iron-deficiency anemia when such doses of iron were discontinued after a month's treatment, when the hemoglobin level had returned to normal and no blood loss was demonstrable. Storage and tissue iron, as well as hemoglobin iron, must be replenished before therapy is terminated.[23] That body iron other than hemoglobin iron is deficient in these patients is evident from many studies.[18-20] It has been shown that iron-containing enzymes are also reduced in iron-deficient animals.[21,26]

Reimann[25] recently presented a vivid illustration of the effects of long-standing

iron deficiency on a whole population, re-emphasizing the fact that depletion of tissue iron as well as decrease in hemoglobin iron and consequent anemia are detrimental to optimum well-being. Brokow and others found that normal infants' height, weight, and muscle tone were improved when iron-containing foods were added to their diets, though hemoglobin values did not rise significantly.[22] Since no investigations have been published documenting the desirability of increasing the normal hematologic values in infants from, e. g., 11 to 13 gm/100 ml., indiscriminate supplementation of "normal" infants' diets is not recommended. Good evidence exists that "iron-loaded" persons may absorb as much orally administered iron or more than do normal subjects.[5,24] † Therapeutic iron is indicated only if specific evidence of iron deficiency exists. The prescription of "shotgun" hematinics for anemia, real or supposed, in infants and children is to be abhorred.

Summary

Balance studies utilizing a radioiron salt (ferrous sulfate) were made in 34 normal and 5 iron-deficient infants and children. The largest single dose of ferrous iron tolerated and absorbed well was 30 mg.

Twelve to fifteen per cent of the 30 mg. doses of Fe^{++} given once or twice a day were absorbed by normal children.

One hundred eighty cubic centimeters of milk or one hundred cubic centimeters of orange juice given with the iron salt resulted in less absorption of iron than when the ferrous sulfate alone was given.

Iron-deficient infants absorb more ferrous iron than do normal infants.

A quantitative approach to the correction of iron-depleted states in infants is presented.

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A Quantitative Study of the Fate of Recently Absorbed Food Iron

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With the introduction of radioactive Fe^{59} as a research tool there has been a greatly renewed interest in the investigation of iron absorption and metabolism. With the use of isotopes it is now possible to differentiate iron administered during a test period from that iron already present in the blood and body tissues or that present in the environment. Many balance studies have been performed to determine the amount of iron absorbed from a test meal under various laboratory and clinical conditions.[1-13] Though it has been noted that most of such iron is incorporated into hemoglobin, a fairly constant discrepancy between the iron found in the stools and that appearing in hemoglobin seemed apparent. Previous balance studies on the absorption of radioactive food iron in humans give little information concerning the fate of recently absorbed iron. The present investigation was undertaken to determine the amount of Fe^{59} detectable in the blood and tissues of normal, iron-deficient, and iron-loaded dogs 14 days after the administration of isotopically labeled food iron.

Methods

Six mongrel dogs weighing 7 to 11 kg. were selected at random from the U. C. L. A. animal pool. The dogs were vaccinated, freed of intestinal parasites, and housed in metabolic cages in a temperature-controlled room. The animals were divided into control, iron-loaded, and iron-deficient groups on the basis of their hemoglobin values. Initial hematologic values are shown in Table 1. The control group was fed a standard ration (one can of Friskies per day) with daily supplements of ¼ lb. of fresh horse meat and 0.6 cc. of a polyvitamin preparation. The iron-loaded animals received a similar diet plus intravenous injections of saccharated iron oxide (Proferrin *), as shown in Table 2. Iron-deficient animals received a milk diet (one can of evaporated milk and water) with supplemental cooked polished rice as needed to control weight loss and diarrhea. The iron-deficient dogs also received repeated percutaneous femoral vein phlebotomies until reticulocytopenia persisted in the face of profound microcytic hypochromic anemia (Tables 2 and 3).

Radioactive test meals fed to the animals consisted of Fe^{59} tagged chicken liver and eggs. Fe^{59} sulfate was injected intravenously into laying hens until eggs and liver with high radioactivity were

TABLE 1.—*Initial Hematologic Values*

Dog	Group	Hgb., Gm./100 cc.	Hct., %	Rbc, Million	Retic., %	Fe, μg./100 cc.	Cu, μg./100 cc.	FEP, μg./100 cc.	Wt., Kg.
131	Control	14.9	39.6	5.18	0.3	--	97	28.1	9.85
137	Control	14.9	40.5	5.37	0.3	74	100	29.4	10.55
132	Fe-loaded	18.4	52.0	6.32	0.1	99	106	31.2	7.1
134	Fe-loaded	15.2	42.5	4.97	0.1	146	103	19.6	11.0
135	Fe-deficient	13.9	42.0	4.94	0.4	107	--	31.2	8.95
136	Fe-deficient	14.1	39.5	4.86	0.2	72	88	36.1	8.65

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* Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

TABLE 2.—*Preparation of Experimental Animals*

Dog Group	Saccharated Fe Oxide Injected, Mg.	Phlebotomy, Cc.	Period of Administration, Days
132 Fe-loaded	1,600	--	27
134 Fe-loaded	1,700	--	27
135 Fe-deficient	--	895	27
136 Fe-deficient	--	1,045	35
131 Control	--	--	--
137 Control	--	--	--

TABLE 3.—*Hematologic Values at Onset of Balance Period*

Dog	Group	Hgb., Gm./100 Cc.	Hct., %	RBC, Million	Retic., %
131	Control	20.0	56.7	6.88	0.2
137	Control	20.8	55.3	7.34	0.4
132	Fe-loaded	19.2	53.5	6.58	0.6
134	Fe-loaded	16.2	43.6	5.11	0.4
135	Fe-deficient	6.0	19.7	3.53	2.4
136	Fe-deficient	5.6	19.5	2.90	3.4

TABLE 4.—*Radioactive Iron Feedings*

Dog	Group	Volume Fed, Ml.	Total Fe Content, Mg.	Total Fe [59] Activity, μc.	Length of Feed Period, Days
131	Control	675	13.73	79	3
137	Control	670	13.70	79	2
132	Fe-loaded	410	9.93	80	2
134	Fe-loaded	410	9.93	80	2
135	Fe-deficient	705	11.68	52	8
136	Fe-deficient	715	11.84	52	8

obtained. The livers were cooked and then mixed with the eggs in an electric blender. The homogeneous mixture thus obtained was analyzed for both total and radioactive iron content. Data on the test meals are presented in Table 4. Quantitative feedings were accomplished by gavage feeding of the animals in the fasting state.

The previously mentioned diets were resumed when the feedings were completed, and the stools were quantitatively collected for a period of 14 days after the completion of the test meal. The stools were then homogenized, wet-ashed by boiling in concentrated H_2SO_4, and analysed for total radioactivity by measurement of γ-radiation of duplicate samples in a deep-well scintillation counter.

Hematologic values at the completion of the 14-day balance period are shown in Table 5.

The dogs were killed on the 14th day after the test feeding. Prior to killing the blood volumes were determined by the Evans blue (T-1824) dye-dilution method.[31] Samples were obtained for determinations of radioactivity in the blood, and γ-radiation from whole-blood samples was measured. The body tissues were then freed of hemoglobin-Fe^{59} by exchange transfusion with citrated whole blood from other dogs until the radioactivity in the blood of the experimental animal was less than 2% of the pretransfusion values. The animals were then killed by exsanguination, and the following tissues were obtained for analyses: bone marrow, liver, spleen, kidney, lung, skeletal muscle, cardiac muscle, pancreas, stomach, intestine, and diaphragm.

In order to differentiate the radioactivity in ferritin from that in hemosiderin, all tissues except bone marrow were separated within 15 hours into water-soluble and water-insoluble fractions in the following manner.[28] The tissues were minced, weighed, and homogenized in an electric blender in a cold room (—20 C) until a homogeneous mixture was obtained. Approximately 10 gm. aliquots were then taken from each organ and extracted with 20 cc. of distilled water for three to five minutes, with use of the microattachment of a Waring Blendor. The homogenate was then transferred to 100 ml. Lusteroid tubes with several washings and centrifuged for 30 minutes at 1400 g (2800 rpm in International Model V). The supernatant solution was decanted, and the precipitate was washed with a volume of distilled water equal to the supernate. This was then centrifuged for 30 minutes at 1400 g, and the washing and supernate were combined. The supernate was evaporated to near dryness and transferred with the washing into 15.75×50 mm. counting tubes. The total insoluble fraction was transferred quantitatively to counting tubes. All specimens were counted for total γ-activity, with use of a deep-well counter. Calculation was then made as to total soluble- and insoluble-fraction activity for each organ on the basis of total organ weight. Skeletal muscle was calculated as 30% of total body weight of the dogs.[28] Bone marrow samples were assayed *in toto* for Fe^{59}. Total bone marrow was considered to be 2.5% of body weight.[27]

TABLE 5.—*Hematologic Values at Completion of Fourteen-Day Balance Period*

Dog	Group	Hgb., Gm./100 cc.	Hct., %	RBC, Million	Retic., %	Fe, μg./100 cc.	Cu, μg./100 cc.	FEP, μg./100 cc.	Blood Volume, Ml.
131	Control	17.8	53.0	6.20	1.2	171	83.3	16.2	732
137	Control	18.6	58.2	6.05	0.1	150	113	21.3	753
132	Fe-loaded	18.1	47.2	5.48	1.0	138	127	38.6	587
134	Fe-loaded	14.8	42.6	4.93	0.1	201	--	35.5	806
135	Fe-deficient	7.3	25.5	4.52	2.0	11	88	93	895
136	Fe-deficient	8.8	29.3	4.46	0.1	3	132	94	853

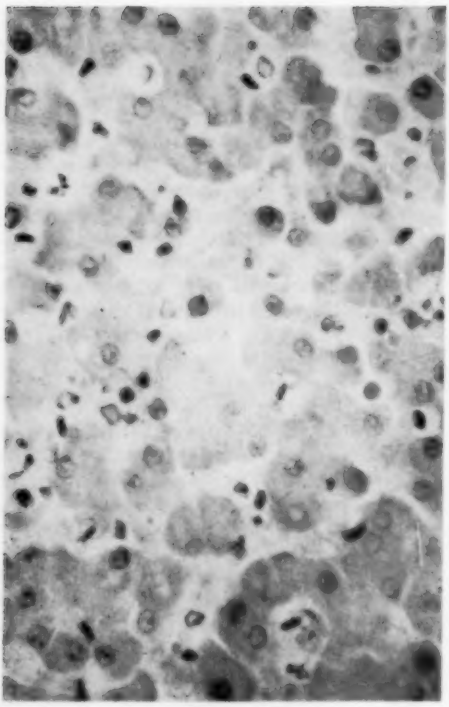

Figure 1

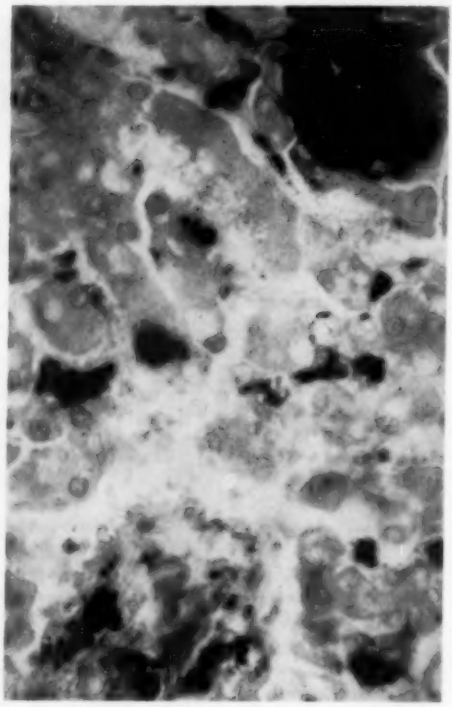

Figure 2

Comment on Method

The preparation of iron-loaded and iron-deficient animals was designed to obtain maximal and minimal iron stores in the respective groups. The administration of saccharated iron oxide in a quantity approximating the total reserve iron of a 70 kg. man assured marked saturation of all iron stores. The extent of this can be seen in Figure 1, showing a liver section, stained with Prussian blue, from one of the iron-loaded animals. The lack of stainable iron in the iron-deficient liver is shown in Figure 2. The repeated removal of blood from the animals on the iron-free diet assures mobilization and depletion of tissue iron stores, whereas acute blood loss, although producing marked anemia, does not assure similar depletion of "storage forms in the length of time allotted to this experiment.

A major problem of this study lay in the method for separating the storage iron from hemoglobin iron. The presence of iron in both ferritin and hemosiderin, two chemically distinguishable substances, has been long recognized. The method of separation based on relative water solubility was outlined by Gabrio et al. in 1953. They showed, by using a method similar to that described above, that 94% of the hemosiderin remained in the water-insoluble fraction and 94% of hemoglobin and 98% of ferritin remained in the water-soluble extract. The method was checked with use of isotope and immunochemical methods and was found to have a reproducible accuracy of 5%. In our attempt to confirm this technique by using radioactive chicken red blood cells added to nonradioactive chicken liver, it was repeatedly found that, at best, only 80% of the hemoglobin-Fe^{59} in the red blood cells could be recovered in the water-soluble fraction. This left a 20% contamination in the insoluble fraction, which would completely mask any activity present in the less-active hemosiderin. Repeated washing

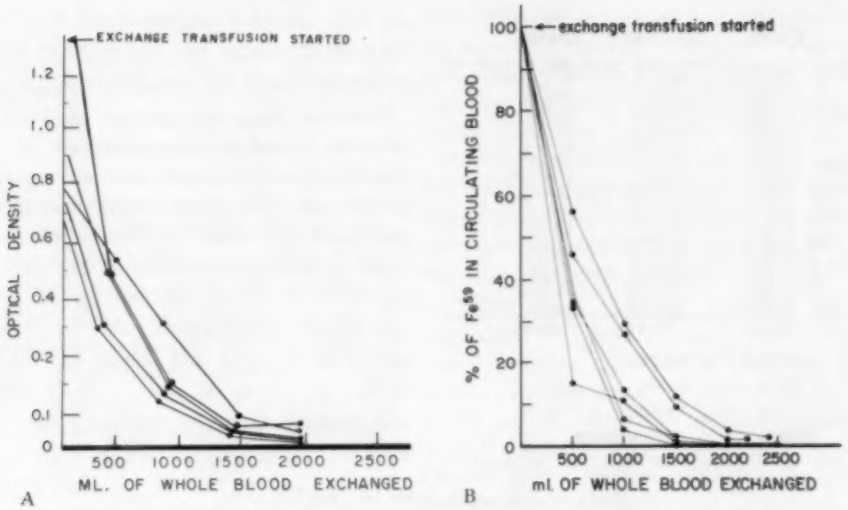

Fig. 3.—*A*, removal of Evans blue by exchange transfusion in dogs. *B*, removal of hemoglobin-Fe^{59} by exchange transfusion in dogs.

and resuspension of the insoluble fraction showed no greater removal of the hemoglobin-Fe^{59} than did the initial washing. However, when Fe^{59}-tagged hemoglobin solution was used instead of the tagged red cells, the extraction yielded 94% of hemoglobin activity in the soluble fraction. This yield corresponds well with that of Gabrio et al. but rendered this process impractical for these experiments that dealt with intact cells. Other investigations have shown that from 2% to 23% of the total red cell hemoglobin is not removed by lysis and water extraction of the cells.[18]

The possibility of using saline-washed or viviperfused organs was considered; it was felt, that minute amounts of tissue activity were attributable to ferritin, which, being a water-soluble fraction, would be partially mobilized and removed from the tissues by this procedure. Since the ferritin yield was expected to be small, this would introduce a relatively large error.

The method finally decided upon was to give the living animals a total whole-blood exchange-transfusion prior to killing. In this manner, nonradioactive blood would be present in the animals at death and hemoglobin-Fe^{59} would not have to be accounted for in tissue and storage iron analyses. The technique used was similar to that used in erythroblastotic infant exchanges in this hospital. Figure 3 shows the amounts of circulating Fe^{59}-tagged blood left at successive stages of the transfusions. It can be seen that the postexchange blood Fe^{59} values are only a very small percentage of the preexchange values. These figures and the Evans blue dye-dilution curves also serve to reaffirm the relatively complete blood exchange which can be obtained with the present techniques.

The methods of animal preparation are self-explanatory. The iron-deficient diet originally used was canned evaporated milk and water. The animals on this diet developed marked diarrhea and associated weight loss. The addition of cooked polished rice to the diet rectified both conditions. The iron content of rice is very low—0.16 mg. Fe/100 gm. rice.[19]

Results

The results of the metabolic balance studies at the end of the 14-day experimental period as shown in Figure 4. From 96% to 103% of the orally administered dose was

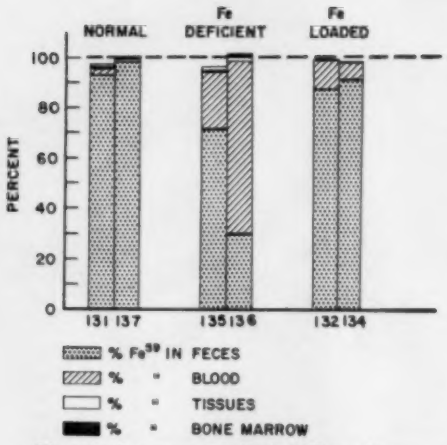

Fig. 4.—Recovery of food Fe^{59} in dogs.

not only absorbed slightly more iron than the control animals but proceeded to incorporate more into the hemoglobin.

Table 6 shows the amount of Fe^{59} activity recovered in the separation of the tissues into water-soluble and water-insoluble fractions. These figures are more simply expressed in Table 7. Though obviously small, a measurable amount of Fe^{59} activity was detected in all tissues. In the iron-loaded and control animals this was limited mainly to the liver and spleen. Of interest is the deposition of iron in both soluble and insoluble forms by the iron-loaded animals.

TABLE 6.—*Tissue Analysis for Iron^{59} Activity*

Dog	Group		Diaphragm	Liver	Spleen	Pancreas	Kidney	Heart	Skeletal Muscle	Lung	Stomach & Proximal ½ Intestine	Colon & Distal ½ Intestine	Bone Marrow
131	Control	Wt.*	53.29	228.71	19.05	20.19	46.11	70.94	2685	72.03	166.45	165.86	224
		S	--	2.2	0.2	--	--	--	--	--	--	--	1.0
		I	--	--	--	--	--	--	--	--	--	--	--
137	Control	Wt.	53.62	225.08	18.67	14.80	45.50	82.81	3000	70.25	181.27	161.20	250
		S	--	4.5	0.5	--	--	--	--	--	--	--	2.5
		I	--	--	--	--	--	--	--	--	--	--	--
132	Iron-loaded	Wt.	48.44	258.04	25.58	15.59	41.57	66.06	2190	58.80	149.96	148.35	283
		S	--	0.4	0.1	--	--	--	--	0.1	--	--	0.4
		I	--	--	0.1	--	--	--	--	--	--	--	--
134	Iron-loaded	Wt.	50.01	211.07	23.20	15.90	52.88	68.38	2925	79.23	178.10	164.98	245
		S	--	0.5	0.1	--	--	--	--	--	--	--	0.5
		I	--	0.1	0.1	--	--	--	--	--	--	--	--
135	Iron-deficient	Wt.	41.33	210.36	16.09	17.65	41.69	48.58	2400	60.60	196.50	167.60	200
		S	--	1.0	0.4	--	0.1	--	0.1	0.1	--	0.4	1.8
		I	--	0.5	(Lost)	--	0.1	--	--	--	--	--	--
136	Iron-deficient	Wt.	47.52	205.87	17.70	23.25	41.03	68.00	3060	78.77	181.60	200.62	115
		S	0.1	0.8	0.1	0.1	0.1	0.1	0.1	0.1	0.1	--	1.8
		I	--	0.3	0.1	--	0.1	0.1	--	--	--	--	--

* Wt., weight in grams; S, soluble fraction as per cent of total absorbed Fe ^{59}; I, insoluble fraction as per cent of total absorbed Fe ^{59}.

recovered in the stool, blood, and tissues of the animals. Of the iron which was absorbed, 95% or more was present in the circulating hemoglobin mass in all animals. The amount of iron absorbed was generally proportional to the state of iron deficiency. The absorption in a given group was similar except in the iron-deficient animals, where a discrepancy is noted. Animal 135 had rather marked diarrhea during the balance study, which could explain the poorer absorption in this animal. It has been shown in balance studies on infants that 93% to 100% of orally administered food iron is not absorbed during episodes of diarrhea.[20] Of special interest in the data of this balance study is the fact that the iron-loaded animals

TABLE 7.—*Tissue Analysis for Fe^{59} Activity* *

		Control		Iron-Loaded		Iron-Deficient	
		Dog 131	Dog 137	Dog 132	Dog 134	Dog 135	Dog 136
Liver	S †	++	++++	+	+	+	+
	I				+	+	+
Spleen	S	+	+	±	+	+	+
	I			±	±		±
Kidney	S					+	+
	I					+	±
Lung	S			±		+	+
	I						
Colon and distal int.	S						
	I					+	
Skeletal muscle	S					+	±
	I						
Heart	S						+
	I						+
Stomach and proximal int.	S						+
	I						
Pancreas	S						±
	I						
Diaphragm	S						±
	I						
Bone marrow		+	+++	+	+	++	++

* + to ++++ indicates 1% to 4%.
† S, water-soluble fraction; I, water-insoluble fraction.

Comment

The fact that between 96% and 103% of the orally administered Fe^{59} could be accounted for in the blood, tissues, and feces of experimental animals on balance studies reconfirmed our previous findings and those of others concerning the accuracy of this method of experimentation. Likewise, the fact that 95% or more of the absorbed iron is present in the circulating hemoglobin mass points out the accuracy in equating hemoglobin activity with iron absorption in radioactive-iron balance studies. It would thus appear that the greatest limitation imposed on the accuracy of determinations of oral iron absorption based on the blood Fe^{59} activity is due to the methods used for calculation of blood volumes.

Of more possible clinical significance is the finding that the iron not only was absorbed in the iron-loaded animals but was absorbed to a greater extent than in the control group. The subject of iron absorption and excretion has been controversial and is as yet unsettled. It is generally agreed that iron excretion is minimal. Dubach et al. have shown a daily fecal excretion averaging 0.3 to 0.5 mg. in normal subjects and ranging from 0.1 mg. in patients with hypochromic anemia to 1.4 mg. in those with hemolytic states.[21] Excretion through the skin has been shown to be insignificant.[22] It seems reasonable that these small amounts of iron loss can be explained by the iron content of normally desquamated cells. Since there is minimal iron excretion, the degree of iron absorption assumes obvious importance. The mechanism of this absorption is still unknown. Granick's original "mucosal block" concept, involving ferritin as a transcellular transport form of iron, is no longer completely tenable.[23] Heilmeyer has recently shown that animals fed iron orally show a maximum mucosal ferritin concentration in 10 days, while the liver iron content gradually increases through a 40-day test period.[24] High mucosal ferritin concentration did not block further iron absorption. From this evidence he concludes that ferritin is a mediator and not a controller of iron absorption.[24] Granick has recently proposed a modified theory based on a relative oxidation-reduction potential difference across the mucosal cells which causes a flow of ionized iron through the cell.[25] It is apparent from this discussion that at the present time no totally acceptable theory on iron-absorption control mechanisms has been presented.

Studies such as are reported here and those of others which show that iron absorption proceeds as well, if not better, in the face of increased iron stores as it does in normal animals strongly suggest that either there is no effective control of iron entrance to the body or the regulatory mechanism is lacking in some siderotic subjects. Because of minimal excretion of iron, parenteral iron compounds should be used cautiously until more is known of the pathology of iron excess. Furthermore, if there is no effective control of absorption of oral iron then this form of iron therapy should also be closely regulated and the long-term use of iron-containing hematinics, placebos, and prophylactic medications should be condemned. Several cases of undeniable hemochromatosis have developed in patients treated in such a fashion.[26,27]

The fact that absorbed radioiron from food was deposited as both soluble and insoluble forms in iron-loaded and iron-deficient animals adds an interesting point to the consideration of iron storage. It must be first pointed out that the division of storage iron into ferritin and hemosiderin by the water-solubility method used[15] is somewhat empirical and is restricted by the experimental limitations of the method. However, well-documented quantitative recovery may be obtained. It is known that ferritin and hemosiderin are biochemically distinguishable on the basis of their staining reactions, crystal formation with cadmium sulfate, electrophoretic patterns, and solubility in water. It has been shown also that both are formed with the apoferritin mole-

cule as a basic building block. Bielig has synthesized ferritin from apoferritin and iron,[24] while Granick has demonstrated apoferritin in the hemosiderin molecule by successive dialyses of the iron portions.[25] It appears possible, therefore, that these two substances are similar in structure and differ only in the amount of iron bound to each. Heilmeyer has stated that ferritin is 20% to 24% iron while hemosiderin is 31% to 36% iron. Thus, there appears to be a spectrum between apoferritin and hemosiderin, with ferritin as an intermediary state defined by experimental conditions. Such a concept was stated earlier by Shoden et al.[29] and allows a simpler explanation of why iron should be deposited in both forms than does the earlier concept of the stable (hemosiderin) and labile (ferritin) iron pools. The distinction between the lability of one or the other compartments is also questioned by Finch, who observed that patients with idiopathic hemochromatosis may utilize liver iron for erythropoiesis.[28]

The widespread deposition of Fe^{59} in the iron-deficient dogs suggests a generalized tissue deprivation of this substance and points out the fact that the anemia is only the most easily demonstrable manifestation of a widespread iron deficiency. When blood volumes of the organs are considered,[30] the measurable radioactivity in these tissues was much more than might have been accounted for by hemoglobin-Fe^{59} left in the tissues during exchange transfusion. Iron and iron-porphyrin compounds are intimately related to vital physiologic functions other than erythropoiesis. Such iron-containing substances are myoglobin; cytochrome A, B, and C; peroxidase, catalase, and flavoproteins, which contain a qualitatively important fraction of the total body iron. Recent work in Neurospora shows that in the iron-deficient state there is a reduction of catalase, peroxidase, succinic dehydrogenase, and isocitric dehydrogenase activity.[31] The effect of this reduction therefore manifests itself over the entire Krebs cycle. Similar enzyme deficiencies were shown in guinea pigs rendered iron-deficient.[32] A disturbance in the action of the tricarboxylic acid cycle to the point of ketosis and a marked decrease in the activity of the mitochondrial enzyme systems of the liver was demonstrated in these animals. Beutler has recently reported that cytochrome C, too, is decreased in iron-deficient animals.[33] When these concepts are related to the clinical picture of iron deficiency in pediatric patients, they may explain the commonly observed general improvement in these patients before appreciable changes in hemoglobin levels have occurred following institution of iron therapy.

Summary

The results of a 14-day metabolic balance study on normal, iron-deficient, and iron-loaded dogs fed food containing in vivo-tagged radioactive iron are given. The tissues of the animals were analyzed for soluble and insoluble radioactive iron, and the amounts of each were determined on the basis of total organ weight. The results of the balance study tend to confirm the accuracy of this experimental method. Ninety-five per cent or more of absorbed iron is present in the circulating red cell mass 14 days after the isotope feeding. The ineffectiveness of any intrinsic iron-absorption regulation in the siderotic subject is emphasized, and the dangers of indiscriminate oral intake are reiterated. Tissue analyses show that some of the recently absorbed food iron is found in both soluble and insoluble forms in all animals and that iron-deficient animals tend to deposit more of such iron in all tissues. Some clinical and experimental implications of these findings are discussed.

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Enteropathogenic Escherichia Coli Diarrhea

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During the fall and winter months of 1955-1956, a study was carried out to determine the possible association of enteropathogenic forms of Escherichia coli (EPEC) with diarrheal diseases in infants and children admitted to the Los Angeles County General Hospital.[1] The results of this survey suggested the presence of an endemic infection in the community with EPEC serotypes, predominantly O111:B_4. Furthermore, the evidence pointed to a secondary spread on the infant wards in the hospital, where greater numbers of infants of susceptible age accumulated.

A second study, covering the early summer months of 1956, was undertaken. However, the serological methods of identification have been extended to conform to the criteria defined by Kauffmann [2] and recently emphasized by Ewing.[3] Despite the fact that earlier recognition of the disease, isolation, and prompt therapy are part of our program now, the EPEC serotypes continue to be seen in approximately the same proportions, suggesting the presence of a reservoir of infection in the community. A description of the characteristics of the sera used for identification of the serotypes, the serological results with prototype strains, and the results of this survey are the purposes of this report.

Material and Methods

Subjects.—During the period covered by the survey, June through August, 1956, a total of 223 stools from 106 infants was examined. The infants selected for this study included only those one year or less in age with signs and symptoms of diarrhea and confined to the acute disease unit of the hospital. Several additional cultures from infants with diarrhea confined to the communicable disease unit were also examined. The stools were obtained from the patients on the wards in "Sealtite" containers and transported to the laboratories for examination. Acute and convalescent paired sera were obtained whenever possible and preserved for subsequent serological studies.

Stool Cultures.—Upon receipt of the stool specimens in the hospital laboratories, suspensions were prepared in 0.85% NaCl solution and plated on routine diagnostic enteric media. The media used for the isolation of the EPEC forms included MacConkey agar, eosin-methylene blue agar, sorbitol agar, and 2% rabbit blood agar. The agar plates were streaked with suspensions of the stools and incubated 18 to 24 hours. Following incubation, the plates were examined for the presence of sorbitol- or lactose-negative forms and also for hemolytic coliform colonies. All sorbitol-negative colonies were transferred to triple sugar slants and incubated for an additional 24 hours.

In those cases where no sorbitol-negative colonies were observed but where the eosin-methylene blue plates confirmed the presence of E. coli, macroscopic slide agglutinations with pooled polyvalent antiserums were employed to select EPEC types fermenting sorbitol. Swipes with a sterile loop giving positive agglutination were transferred to triple sugar slants; those which agglutinated with the polyvalent sera were restreaked on sorbitol agar and incubated for isolation and typing with monovalent sera.

Triple sugar slants showing characteristic fermentative reaction for E. coli were further tested with monovelent O antisera, diluted 1:10. These tests were macroscopic slide agglutinations. Organisms which gave 3+ or 4+ reactions were transferred to nutrient agar slants for final identification by use of O monovalent sera in tube-dilution tests with heat-killed organisms.

Preparations of Antisera.—The antisera used against the specific strains were prepared by the method of Edwards and Ewing,[4] although certain modifications in dosage were made. It was found necessary to reduce the amount of the initial injections, particularly with the O55:B_5 and O111:

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TABLE 1.—*Specificity of OB EPEC Antisera*

E. Coli Serotype	OB Antibody Titer	O Antibody Titer	OB Agglutination (1/10-Dilution Slide Test)							
			26	55	86	111	119	125	126	127
O26:B$_6$	640	2560	++++	--	--	--	--	--	--	--
O55:B$_5$	640	2560	--	++++	--	--	--	--	--	--
O86:B$_7$	320	640	--	--	++++	--	--	--	--	--
O111:B$_4$	320	2560	--	--	--	++++	+	+	--	--
O119:B$_{14}$	5120	1280	--	--	--	+	++++	+	+	--
O125:B$_{15}$	20480	640	--	--	--	+	+	++++	--	--
O126:B$_{16}$	320	5120	--	--	--	+	--	--	++++	--
O127:B$_8$	320	20480	--	--	--	--	--	+	+	++++

B_6 strains, to prevent severe or fatal endotoxic reactions. For the production of both O and OB antigens, smooth colonies of the serotypes O26:B_6, O55:B_5, O86:B_7, O111:B_4, O119:B_{14}, O125:B_{15}, O126:B_{16}, and O127:B_8 were selected.* A number of pharmaceutical companies now have commercially available antisera for some of the EPEC serotypes.

The antigens used to immunize for the OB antisera were prepared from 18-hour agar slants. Suspensions were made in formalinized saline for the first five injections and in istonic saline for subsequent injections. The suspensions were adjusted to the density of a No. 1 MacFarland nephelometer reading. The rabbits received a series of biweekly injections by the intravenous route ranging in volume from 0.1 ml. to 1.0 ml.

The antigens used for the production of O antisera were also prepared from 18-hour slants. Suspensions were made and heated at 100 C for two and one-half to three hours to insure inactivation of the B and H antigens. After heating, the suspensions were cooled and adjusted to a No. 1 nephelometer density with formalinized saline. The protocol for the preparation of O antisera consisted of a bi-weekly series of intravenous injections, 0.5 ml. to 2.0 ml., covering a period of three weeks.

The final titers and specificity of the antisera were assayed in tube-dilution tests with use of both O and OB antigens. Monovalent OB antisera for the slide agglutinations were diluted 1:10. Pooled polyvalent OB antisera for the screening tests were diluted 1:5. Two polyvalent pools were prepared, one containing antisera for O26:B_6, O55:B_5, O86:B_7, and O111:B_4 serotypes; the second pool contained the higher-numbered serotypes and included O119:B_{14}, O125:B_{15}, O126:B_{16}, and O127:B_8. Some of the sera and antigens produced for this study were compared with specific absorbed sera against O26:B_6, O86:B_7 O111:B_4, and O127:B_8.† The results showed good agreement between the two sets of sera.

Serological Identification.—Those isolates which gave 3+ or 4+ reactions in either of the two pools of polyvalent sera were then tested, and, if they gave similar results with the OB monovalent slide test, they were further identified in the following fashion. Agar slants inoculated from the triple sugar slants were incubated 18 to 24 hours. Suspensions were then prepared from the slants and heated for two hours at 100 C. The suspensions were cooled, adjusted to the density of a No. 3 nephelometer standard, and used as antigens for O agglutinations. Initial tests were performed in this manner with the OB antisera, while later tests were done with O antisera. However, cross tests on the same antigens with both O and OB antisera showed that the O titers of the OB antisera were sufficient for diagnostic purposes. The dilution series were twofold tube agglutinations starting with 1:20 and carried through 1:320. They were incubated overnight at 50 C and read in the usual manner.

Results

The titers of the antisera used in identification of the EPEC serotypes are shown in

* Obtained from Dr. W. W. Ferguson, Michigan State Department of Health Laboratories, Lansing, Mich.

† These sera were obtained from Dr. C. W. Christenson, of the Difco Laboratories, Detroit.

TABLE 2.—*Specificity of O EPEC Antisera*

E. Coli Serotype	O Antibody Titer	OB Antibody Titer	O Agglutination (1/10-Dilution Slide Test)							
			26	55	86	111	119	125	126	127
O26:B$_6$	20480	20	++++	--	--	--	--	--	--	--
O55:B$_5$	640	40	--	++++	--	--	--	--	--	--
O86:B$_7$	640	40	--	+	++++	--	+	--	--	--
O111:B$_4$	320	--	--	+	--	++++	+	--	--	--
O119:B$_{14}$	640	20	--	--	--	+	++++	--	--	--
O125:B$_{15}$	5120	160	--	--	--	--	--	++++	--	--
O126:B$_{16}$	20480	20	--	--	--	+	--	--	++++	--
O127:B$_8$	10240	160	--	--	--	+	--	+	++	++++

Tables 1 and 2. Little difficulty was encountered in the production of high-titered antisera. The variations observed are probably a reflection of the rabbits used to develop the antibodies. Furthermore, six of the eight antisera developed against the OB antigens had higher titers against the O antigens than against the B antigen. Results of the slide tests showed some slight cross reaction occurring with the higher-numbered serotypes. In addition, occasional nonpathogenic E. coli types showed 1+ or 2+ reactions in the slide-agglutination test. Under such circumstances, the tests were recorded as negative, and only 3+ or 4+ reactions were considered significant. The characteristics of the O antisera, shown in Table 2, reveal little OB antibody and a wide range in O antibody response of the individual strains. Again, slide-agglutination tests showed slight cross reaction in the higher-numbered serotypes. None of these sera were absorbed.

The occurrence of 1+ and 2+ reactions in the slide test with both the OB and O antisera is not of much significance in terms of identification of specific serotypes. Nevertheless, these represent findings that deserve some comment. In cross agglutination tests by the tube-dilution method with the unabsorbed monovalent O antisera against the O antigens, results similar to those recorded in the slide tests were observed. Only in a few instances were titers of 1:40 obtained, and none above this, for the heterologous tests. The O111:B_4 antiserum against O119:B_{14}; the O119:B_{14} against O111:B_4 and O125:B_{15}; lastly, the O125:B_{15} antiserum against O111:B_4 and O119:B_{14} gave titers of 1:40. The findings with all three types of tests—OB slide tests, O slide tests, and O tube-agglutination tests—all showed similar results. Furthermore, only O26:B_6 and O55:B_5 were free of any evidence of cross agglutination by any test. The higher-numbered types tended to give more cross agglutination, but it should be emphasized that these tests were only 1+ or 2+ in the slide test, and the titers achieved are mentioned above. Furthermore, such reactions can be removed by absorption of the antisera with the heterologous organisms. Despite the fact that these reactions were minimal, it suggests that there is some evidence of interrelation of serotypes, most pronounced in the higher-numbered members.

TABLE 3.—*Monthly Summary of EPEC Isolations from Infant Stools*

	Total Cases	Cases Positive for EPEC	% Positive	Predominant Organism	% Positive Due to Predominant Organism
June	12	6	50	O111:B_4	67
July	30	14	48	O55:B_5 O111:B_4	21
August	64	16	25	O127:B_8	33
Total	106	36	30	O111:B_4	50

The total number of infants with diarrhea from whom stools were examined is shown in Table 3. It should be stated that in a great majority of positive stools, where pathogenic types were found, pure cultures of the pathogen were commonly observed. As can be seen, 6 of 12 cases examined in June were positive, 14 of 30 cases in July, and 16 of 64 cases in August. The percentage of positive cases is rather high, showing a maximum during the month of June. In June the most commonly recognized serotype was O111:B_4. July showed O55:B_5, O111:B_4, and, for the first time, O127:B_8. In August O127:B_8 became predominant. The results of the isolations of the individual types during the three months of the study are shown in Table 4. These data also include 10 isolations from infants in the communicable disease unit. While O111:B_4 was the predominant serotype encountered, O55:B_5 and O127:B_8 were also

TABLE 4.—*Monthly Recovery of EPEC Strains from Infant Diarrhea Stools*

EPEC Serotype	Cases, No.			% of Total
	June	July	August	
O26:B_6	1	0	2	8
O55:B_5	0	3	1	11
O86:B_7	0	0	1	3
O111:B_4	4	3	2	25
O119:B_{14}	0	0	1	3
O125:B_{15}	1	2	2	14
O126:B_{16}	0	1	0	3
O127:B_8	0	3	5	22
Other	0	2	2	11
Total	6	14	16	

encountered frequently. The incidence of the other serotypes is also presented in this Table and emphasizes the problem of specific serotyping.

Two strains giving 3+ reactions in the slide tests with the OB antiserum of O111:B_4 did not agglutinate with the specific monovalent O antiserum. All of the other isolates tested showed good agreement between the OB slide test and the O tube-agglutination titers, although a number of specimens when tested against the monovalent OB antisera in the slide test would give 1+ or 2+ reactions. These were shown to be nonspecific when checked with the monovalent O antisera.

A significant number of sorbitol-fermenting EPEC types were encountered in this study. Of the 26 strains isolated in our laboratory, 6, or 23%, were sorbitol fermenters. Two of the sorbitol-fermenting EPEC types were O55:B_5; one each was O125:B_{15} and O126:B_{16}, and one was not clearly typed.

Comment

The data obtained from the cases studied in this survey indicate both the endemic and the epidemic nature of infection with EPEC types in an infant population. Other studies have described the recovery of EPEC types from asymptomatic adults [5,6] and premature infants.[7] The latter might have developed the disease if left untreated. Such findings point to a widespread circulation of the pathogenic E. coli types in some communities. In our experience, the sporadic isolation of some of the strains contrasts sharply with the frequent recovery of O111:B_4, O55:B_5, and O127:B_8. The epidemic nature of EPEC infections is well demonstrated with the O127:B_8 serotype. The strain was not encountered in a previous study [1] but was found in 8(26%) of the cases occurring during July and August. In the later part of July O127:B_8 was isolated from the stool of one infant admitted to the communicable disease unit. In August this particular serotype was found in the stools of five more infants, suggesting a minor outbreak.

The results showing minimal degrees of cross reactions between the eight serotypes used in this study suggest some sharing of antigenic components. In this respect, they offer interesting possibilities in terms of the genetic composition of members of the E. coli group.

Reliance on the use of sorbitol agar as a primary tool in the identification of EPEC is not feasible. However, the use of polyvalent pooled sera for preliminary testing, as has been described, gives reliable results and is the only method recommended. Nevertheless, in those instances where a sorbitol nonfermenter is the principle cause of an epidemic, it may have some value as a means of preliminary identification,[8] but only if confirmatory serological procedures are carried out.

Conclusions

During the summer months of June, July, and August, 1956, a total of 106 infants with diarrhea were examined for the presence of enteropathogenic E. coli. A total of 36 cases was found in which EPEC was isolated from stools. The specific serotype O111:B_4 accounted for 25% of the cases, while an outbreak due to O127:B_8 accounted for 22%.

Approximately 25% of the above-mentioned isolated EPEC types were sorbitol nonfermenters.

Summary

The results of a survey on the occurrence of enteropathogenic Escherichia coli in the stools of infants with diarrhea is described. In the survey, 106 infants were examined, 36 of these, or 30%, were positive for EPEC. The predominent organism encountered in the 36 cases was O111:B_4, but an outbreak due to O127:B_8 accounted for 8 of the 36 cases. Of the 36 strains of EPEC isolated, 6 were capable of fermenting sorbitol.

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A Study of the Hearing Level Following Severe Poliomyelitis

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Disturbance of the special senses are rarely described as being associated with poliomyelitis.[1,2] This has been true in spite of demonstrable central nervous system lesions that would suggest such a possibility.

As early as 1894 Redlich[3] stated that, of all the pontine structures, the lateral vestibular nucleus (Deiters') and the acoustic nucleus were the most severely damaged in bulbar poliomyelitis. Matzke and Baker,[4] in a report dealing exclusively with the effects of poliomyelitis on the pons, found this part of the brain to be involved in "practically every one" of the 109 cases of bulbar poliomyelitis examined pathologically. This damage consisted primarily of a diffuse interstitial-cell infiltration and neuronal damage. In approximately one-third of the cases there were moderate to severe inflammatory changes within the vestibular nuclei, and in five of these the changes had progressed to actual tissue necrosis. Other reports also deal with damage to pontine structures.[5-7] Kino,[6] Horanyi-Hechst,[7] and Swan[8] all noted that the severest damage in pontine structures occurred within Deiters' nucleus. Swan found this nucleus to be involved in each of the eight cases he studied, with at least half of the cells showing neuronophagia and chromatolysis.

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Matzke and Baker commented that although clinically the facial nucleus appeared to be the most prominently involved in pontine poliomyelitis pathologic studies revealed severer damage to other pontine structures. They pointed out that many of these structures were relatively silent clinically and that, since these patients with bulbar poliomyelitis are extremely ill, our clinical observations are often inaccurate and do not present the complete picture of the severity of tissue involvement.

A careful survey of the literature revealed no previous reports of audiometric studies having been done on patients with severe paralytic poliomyelitis, and it is difficult to evaluate the few reports of deafness following poliomyelitis. In 1915 Collier[9] reported a case of "pontine polioencephalitis in an 8-year-old child who had a sudden acute febrile illness associated with convulsions and followed by deafness." Hall[10] in 1918 reported a 10-year-old child who had a febrile illness and spinal fluid findings compatible with poliomyelitis. Her illness was associated with strabismus, facial paralysis, deafness in the right ear, visual disturbance, nystagmus, and "Babinski, right side." This case also had features that did not resemble acute poliomyelitis. In 1927 Busacca and Tomassini[11] reported the case of a 4-year-old girl who became deaf and partially paralyzed following an acute febrile illness that was clinically indistinguishable from poliomyelitis.

An observation of one patient with a noticeable hearing impairment for conversation prompted organization of a study which might reveal further information on the hearing status of a group of patients with severe poliomyelitis.

I. Clinical Material

Thirty-seven extensively paralyzed poliomyelitis patients underwent detailed audiologic assessment in order to determine the precise status of auditory acuity. They ranged in age from 5 to 37 years, with a median age of 17. The mean age was 20, and only five of the group were under 10.

All patients had moderate to severe degrees of respiratory failure, and the great majority had been disabled for several months. The per cent of total paralysis varied from 20 to 92,[12] and therefore all patients were either completely bedridden, confined to the wheel chair, or ambulatory for only a few hours each day. The duration of disability in the group varied from 1 month to 16 years. All patients had some degree of respiratory failure, as evidenced by the fact that losses in vital capacity ranged from 5% to 95%. Approximately half of the patients had been completely weaned from respiratory aids at the time of testing, and the remainder were using respiratory aids for a portion of the 24-hour period but were breathing unassisted when actual testing was in process. The patients on part-time respiratory assistance used various combinations of such aids as the rocking bed, cuirass, and tank respirators.

Criteria for selection of patients to be tested was that the patient be of sufficient age to be cooperative in subjective audiometry, that he be able to breathe unassisted long enough for the audiologic analysis to be completed, and that he be a patient of the Poliomyelitis Respiratory and Rehabilitation Center. It should be emphasized that this represents a select group of patients, in that all were extensively paralyzed. This is further emphasized by the fact that they were referred to the Respiratory and Rehabilitation Center from 10 states.

II. Procedures

The first 25 subjects were tested in sound-isolated chambers of an audiology clinic, each patient undergoing on audiologic analysis which consisted of pure-tone air- and bone-conduction audiometry and speech reception and speech discrimination tests. The remaining 12 consecutively tested patients did not have speech-hearing measures, since this subgroup included many severely involved patients who could not be moved a great distance from the Rehabilitation Center. Their pure-tone tests were done in a quiet room near their hospital division. All testing was done by clinical audiologists from the staff of the Bill Wilkerson Hearing and Speech Center.

Two commercial pure-tone audiometers were used for pure tone testing. An ADC 50 E-2 was used for the first 25 subjects, while a Maico F1 portable audiometer was used for the 12 patients tested in the hospital. Standard audiometric techniques were employed to obtain air-conduction thresholds for each ear in octave intervals from 125 through 8000 cps and bone-conduction thresholds from 250 through 4000 cps. Because of diminished respiratory reserve in many of the patients, it was not considered feasible to utilize masking techniques for bone-conduction tests.

A speech-reception threshold in decibels re normal threshold and an auditory discrimination score in percentage for each of the first group of patients were obtained binaurally. Speech-hearing testing was done by monitored live-voice technique, and through the use of a Panacoustic Hearing Evaluator (Model HE-200) with a talkback channel in a two-room testing suite. The Harvard Spondaic Words and Phonetically Balanced Lists were used for the speech test material. For the last 12 patients, tested in the hospital, only pure-tone hearing acuity (air and bone) was tested.

The 0 db. reference level with which hearing thresholds of subjects in the present study were compared represented "normal threshold of audibility," as defined by the National Bureau of Standards and the American Standards Association.[13] Manufacturers of commercial audiometers are required to conform to this standard. In addition, the performance of the audiometers used had been assessed regularly (semiannually) by calibration in reference to normal ear thresholds for both air and bone conduction. Similar calibrations had been maintained for the speech audiometer system. The two pure-tone audiometers and the speech audiometer had been in use clinically over a three-year period. Intracomparisons of results obtained from both normal and hearing-impaired subjects had shown consistently good clinical agreement between the three testing instruments.

III. Results

The results obtained from the present study are of interest primarily because of the consistent deviation from the normal threshold of audibility shown by this selected group of patients. In evaluating the significance of their hearing levels it is pertinent to point out that the amount of hearing handicap, as such, was not the chief factor of interest. It is well known that in measurement of hearing acuity by pure-tone audiometry a normal-hearing person may, and often will, deviate as much as 10 to 15 db. at one or two frequencies. When all, or nearly all, of the pure-tone thresholds depart from the 0 db. reference

TABLE 1.—*Mean Air-Conduction Thresholds in Decibels in Comparison with Normal Threshold for Three Groups of Subjects*

	Frequency, cps						
	125	250	500	1,000	2,000	4,000	8,000
ADC Audiometer							
30 subjects without poliomyelitis	−1.1	0.7	−1.3	0.6	1.1	−0.3	−0.3
Maico Audiometer							
20 subjects without poliomyelitis	−0.1	0.1	−0.5	−0.1	2.1	−2.0	−1.5
37 subjects with poliomyelitis	12.2	14.5	13.6	14.5	12.8	15.6	5.8

level by as much as 10 db., however, some depression of hearing acuity is indicated, and such audiograms can possess diagnostic value in suggesting certain middle ear conditions, such as those caused by Eustachian tube obstruction by adenoid growth or by early otosclerotic processes. In the present study bone conduction results were very close to those of air conduction, however, and did not suggest a primarily conductive involvement.

While no prepoliomyelitis audiograms were available for the 37 patients, the deviation from average normal hearing appeared to be more than coincidence when test results were compared with those obtained during the same period on two groups of young adult subjects who had not had poliomyelitis. Mean pure-tone thresholds for air conduction for the two groups of subjects, together with the mean thresholds for the poliomyelitis patients, are presented in Table 1. Separate results for each of the two audiometers used in testing the poliomyelitis patients are given for the subjects who had not had poliomyelitis.

The above values demonstrate that the group mean hearing levels for the control subjects adhered extremely closely to the 0 db. reference level, denoting normal threshold of audibility. The age range for both groups was 18 to 30; the mean age was 23 years for the first group in Table 1 and 23.9 years for the second. As stated previously, the mean age for the patients with poliomyelitis was 20 years. The age range for the latter was somewhat greater, but presbycusic hearing loss was not considered to be a factor, since only seven of the group were over 30, and none was older than 37 years. Furthermore, the presbycusic pattern of steadily increasing loss for higher frequencies was not apparent, and losses for any of the frequencies lower than 2000 cps expected with age do not exceed 5 db. for populations under 40.[14]

Inspection of the pure-tone and speech thresholds for the patients with poliomyelitis revealed that more than three-fourths (28) showed at least a slight depression of acuity which would be considered deviant from the norm. There was evident, furthermore, a markedly consistent pure-tone audiometric pattern across the frequency range. This pattern was more uniform from patient to patient than is commonly encountered in a similar number of subjects with hearing loss, and the hearing curves for each patient tended to be very similar bilaterally.

In considering for each patient the six thresholds in the speech frequency range (500, 1000, and 2000 cps for both right and left ears), there was a total of 222 such pure-tone thresholds for the group. Only 10 of the 37 patients demonstrated as many as three or more of the six possible thresholds in this range as good as 5 db., and only seven patients had no thresholds among these six as great as 15 db. Twenty-four of the thirty-seven exhibited three or more threshold levels of the six possible in the two ears equal to or exceeding 15 db., and of the total 222 speech-frequency pure-tone thresholds, 57% were 15 db. or greater.

An illustration of the typical pattern of hearing demonstrable in these patients is seen in Figure 1. In this case the right-ear thresholds are almost identical to the mean thresholds for the entire group. This patient's hearing in the contralateral ear was essentially the same as for the right, with one threshold of 10 db. at 2000 cps, which

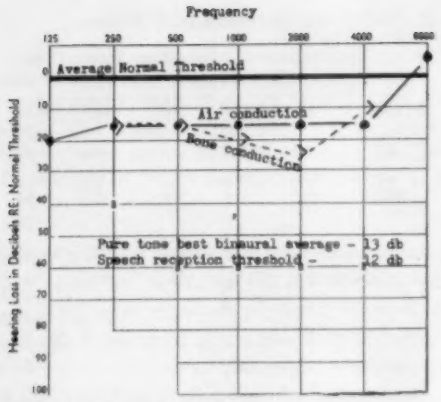

Fig. 1.—Pure-tone audiogram of a 16-year-old white youth. Right ear air- and bone-conduction thresholds typify characteristic audiogram in the severe poliomyelitis patients studied.

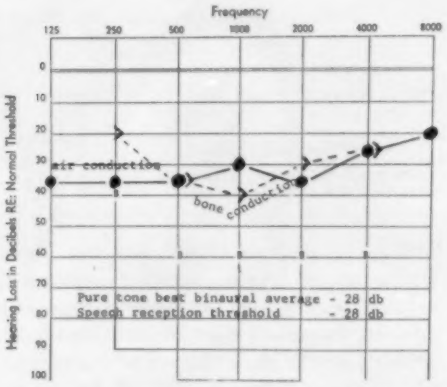

Fig. 2.—Pure-tone audiogram of a 36-year-old white woman. Right (poorer) ear air- and bone-conduction thresholds demonstrate a greater degree of hearing loss than the group average.

resulted in the best binaural average (BBA)* of 13 db. noted below the audiogram curve. This rather uniform depression of hearing across the frequency range except for the return to or near the zero reference level at the high tones was a common finding. Both bone and air conduction was lowered, suggesting either inner ear or retrolabyrinthine involvement.

The audiogram in Figure 2 represents an example of greater hearing loss in the group. While this level of hearing does not represent a serious handicap, it is one at which some communication difficulties are apparent to the patient in group situations and in distance hearing. This patient was experiencing impaired hearing and gave no history of such trouble prior to her illness.

Seven of the thirty-seven patients showed a typical acoustic trauma, or "noise exposure," type of audiogram notch. Their audiograms (example in Fig. 3) were similar to the typical pattern for other poliomyelitis patients (Fig. 1), except for the sharp dip in the curve at the 4000 cps frequency. The 4000-cycle notch is known to be one of the first indications of a hearing problem resulting from noise exposure.[15] The seven patients showing this notch were adult men, several of whom were known to have had excessive noise exposure during military experience. It has been observed previously that this notch is more frequent in males, who are more apt to be exposed to damaging levels of noise in industry, in military life, and in hobbies, such as skeet shooting and hunting. Whether or not these seven patients did or did not have an elevated threshold at 4000 cps prior to their illness can only be conjectured. The question is raised here because of the way in which the observed notch affected the mean group level at this frequency. When these seven

* Average of the best hearing by either or both ears at frequencies of 500, 1000 and 2000 cps.

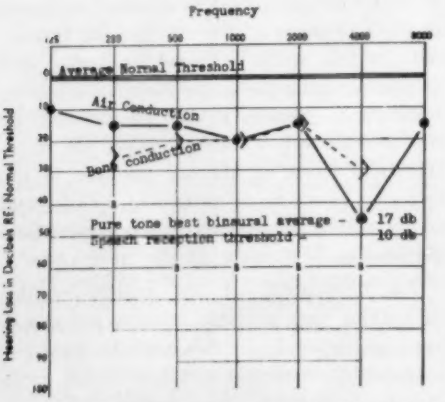
Frequency
Average Normal Threshold
Air Conduction
Bone conduction
Pure tone best binaural average - 17 db
Speech reception threshold - 10 db
Hearing Loss in Decibels RE: Normal Threshold

Fig. 3.—Pure-tone audiogram of a 32-year-old white man. Right ear air- and bone-conduction thresholds of patient reporting previous history of noise exposure (acoustic-trauma notch superimposed on "polio curve").

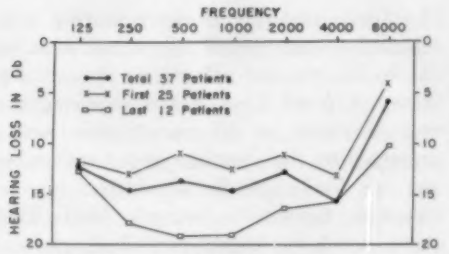

Fig. 4.—Mean air-conduction hearing-loss curves for 37 patients with poliomyelitis.

persons' thresholds were removed, the mean level at 4000 cps dropped to 11.8 db. for the remaining 30. The standard deviation changed from 11.5 db. to 8.5 db. The latter standard deviation was much more comparable to those at the other six air-conduction frequencies, which ranged from 5.7 to 8.4 db.

Since the experimental population consisted of two subgroups with reference to testing conditions, the results for the first 25, tested in the audiology clinic, and those for the remaining 12, tested on the hospital ward, were considered separately as well as together. The general similarity of the audiometric patterns for the two subgroups and the total group is evident in Figure 4. The more marked hearing loss in the latter subgroup is interesting, since six, or one-half, of this number were so severely involved with poliomyelitis that, though they were completely cooperative, their removal to the audiology clinic was considered hazardous. The effect of the 4000 cps notch exhibited by the seven male patients previously mentioned in relation to acoustic trauma exerted its influence on the mean audiogram for the group. Six of these seven patients were in the first subgroup. The rising pattern in high tones began at 4000 cps for the group as a whole, as is indicated by a mean threshold of 11.8 db. for the 30 patients, exclusive of the seven audiograms indicative of acoustic trauma.

The distribution of hearing loss incidence by frequencies is more graphically represented in Figure 5. The greatest incidence of thresholds apparently occurred between

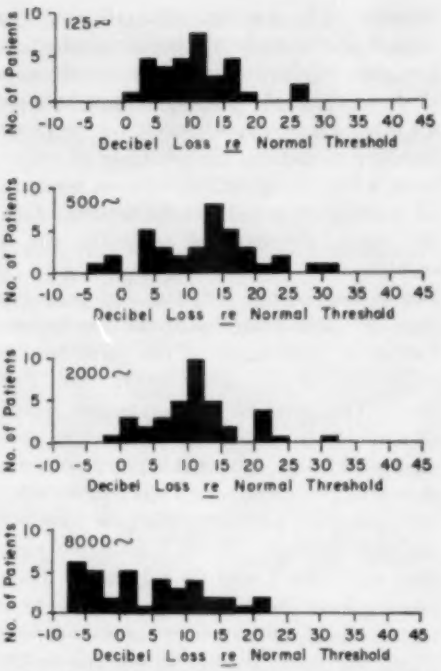

Fig. 5.—Pure-tone air-conduction hearing-loss distribution in 37 patients with poliomyelitis.

10 and 15 db. for the alternate octaves 125, 500, and 2000 cps. This was in contrast to the 8000-cycle tone, where the distribution of thresholds tended to cluster toward completely normal hearing acuity on the left. A neural type of hearing loss was present in almost all cases, as evidenced by close agreement between air and bone thresholds. The standard deviations for bone-conduction thresholds ranged from 6.0 to 8.7 db. and were consequently no less variable than air-conduction thresholds, for which the standard-deviation range has already been noted.

Table 2 presents a comparison of three measures of hearing acuity for the first 25

TABLE 2.—*Comparison of Three Measures of Hearing Loss in Decibels for First Twenty-Five Patients with Poliomyelitis*

	Mean	Diff.	S. E.	Probability
Speech-reception threshold	7.4			
Pure-tone air-conduction best binaural average	9.2	1.8	0.93	0.06
Pure-tone bone-conduction best binaural average	8.7	0.5	0.92	0.52

subjects. The findings illustrate that for these subjects the levels for air conduction, for bone conduction, and for speech were all closely related. This agreement between the three sets of measurements for the group appeared to confirm the reliability of the results, while the agreement between bone and air hearing suggested that the deviation from the normal threshold of audibility was of cochlear or retrolabyrinthine origin. It should be pointed out that the pure-tone data in Table 2 are based on best hearing (either or both ears) at the three speech-range frequencies (500, 1000, and 2000 cps). This level by air conduction would, of course, be expected to correlate most closely with a binaural speech-reception threshold. One may note a discrepancy when comparing the air-conduction pure-tone best binaural average (9.2 db.) with the mean data in Table 1 and in Figure 4. Those hearing levels, however, were based on hearing thresholds of both ears for each patient. Thus, the mean average in the speech-frequency range for both ears was 13.6 db., compared with a best binaural average of 9.2 db.

IV. Comment

The hearing acuity demonstrated by 37 patients severely paralyzed following poliomyelitis was indicative of some reduction in sensitivity to auditory stimuli. This reduction may be peculiar to poliomyelitis or may possibly occur in other conditions where similar complications exist. Numerous factors were considered in an effort to clarify the etiologic significance of these findings.

After careful study, factors such as age, sex, and possible drug therapy were not thought to influence these results. It was believed, in this series of patients, that depressed hearing responses could not be attributed to emotional disturbances or lethargy accompanying serious illness, since they gave oral responses to speech-hearing tests which required more physical energy than the effort required for signaling in response to pure-tone stimuli. Also, those 25 subjects undergoing speech-hearing tests achieved a mean speech discrimination score of 94.2% on the Harvard Phonetically Balanced Word Lists, a test requiring the oral repetition of 50 monosyllabic words presented by the examiner at a comfortable but not loud (25 db. above the speech-reception threshold) listening level. This score, which represents normal discrimination capacity, is additional evidence of their physical ability to carry out test responses and is as good as would be anticipated from testing 25 subjects with comparable hearing levels and in a state of normal health.

It was found that the duration of disability did not correlate well with extent of hearing loss. Sixteen of the twenty-two subjects with deviations from normal greater than 10 db. were patients who had been ill for less than 15 months, and five of the fifteen with hearing levels under 10 db. had been ill less than 15 months. It was difficult to associate the effects of prolonged recumbency with the test findings, but studies are being continued in this regard. Certainly, several patients who were ambulatory and others who were in a wheel chair throughout the day demonstrated this same defect. In order to compare extent of paralysis with hearing loss, a comparison of disability expressed in per cent of total paralysis [12] with decibels of loss expressed as best binaural average was made. No definite relationship could be observed.

A significant correlation, however, was observed between loss in hearing and loss in vital capacity. Thus, patients with marked decrease in vital capacity were apt to show significantly greater hearing loss. This was especially true if one eliminated the few patients who had been ill less than six months. The significance of this is not clear, and it may be only a reflection of the severity of the disease in a particular patient.

In regard to the above finding, one can only speculate as to the possibility that hypoxia following decreased vital capacity and its effect on the central nervous system may have played a part in producing this

defect. This observation also might lead one to suspect that respiratory aids may have caused auditory damage because of vascular pressure changes or because of a noise element. It was not possible to relate the loss of hearing to duration of respiratory assistance, type of respiratory aid, or the time interval since patients had last used their respiratory equipment. It was interesting to consider other possible aspects of this noise element. It did not appear that the hearing defect was the result of acoustic trauma, since the noise of the respirator was not of an intensity considered damaging † and since the audiometric contour was not that customarily seen in acoustic trauma.[15] The possibility was considered that patients might be subconsciously rejecting certain sound frequencies which had been produced by their respiratory aids. This theory, however, did not seem reasonable in the light of the fact that the deviation in hearing levels demonstrated encompassed the frequency spectrum that would include predominant octave bands of almost any environmental sound. Furthermore, several patients who had been without respiratory aids for several years demonstrated the greater elevation of thresholds.

Inspection of the test data suggests that an auditory lesion, if present, involves the neural elements of the auditory mechanism either directly or indirectly. The uniformity of the pattern and the bilateral consistency would suggest that the lesion is most apt to be between the inner ear and the auditory receptor in the cortex.

Summary

A deviation from normal threshold of audibility was found in a group of patients severely paralyzed following poliomyelitis. Because there are many other clinical symptoms more distressing to the patient and physician, and since communication with such patients is usually at close range, such reduction in sensitivity can be easily overlooked even when it reaches moderate proportions of severity. The etiologic significance of this finding is not clear.

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† Over-all noise level measured with a General Radio Sound Level Meter, Type 1551-A, did not exceed 62 db. with one cuirass, one rocking bed, and two tank respirators in simultaneous operation.

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Prochlorperazine as an Antiemetic in the Severely Retarded Child

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Introduction

Emesis can be considered an almost universal symptom in pediatric practice, and an enumeration of its causes would encompass the whole field of medical practice. The mechanism of vomiting has not been satisfactorily explained. A vomiting center [1] has been postulated in the dorsolateral border of the reticular formation of the medulla oblongata. Closely associated are centers for inspiration-expiration, vasomotor control, salivary control, spasmodic respiration, vestibular control, and bulboexcitatory and inhibitory control. The vomiting center [2] receives stimuli from the floor of the fourth ventricle, the viscera, the diencephalon, and other forebrain structures.[3] Emetic impulses may originate in the periphery or in the central receptor areas, the impulses passing through the vomiting center to the terminal pathway and exerting influence on the previously mentioned coordinating centers. Vomiting is, therefore, a patterned response of several centers coordinated through the vomiting center. The immediate cause of vomiting is frequently difficult to establish and is not necessarily a symptom of an obviously presenting disease. In some instances, the vomiting may be more distressing than the disease with which it is associated. This is not uncommon in institutions for severely retarded children, where a large number of chronically diseased children with various acute exacerbations are domiciled.

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Many antiemetic drugs have been used symptomatically in an effort to control chronic vomiting. Some act on foci where emetic stimuli originate; others block pathways conducting emetic impulses or act upon the vomiting center itself. There may be a combination of these actions, or the actions may be on related centers, such as the labyrinth or the autonomic centers.

The antiemetic properties of the phenothiazines were noted during the study of their pharmacology. Apomorphine-induced vomiting in animals was inhibited by prochlorperazine.[4] Investigations in human beings have shown this drug to be five times more potent than chlorpromazine, and small doses produced the same result as larger amounts without the same incidence and severity of side-effects. It is believed [5] that the action is on the reticular formation of the medulla oblongata, affecting both the vomiting center and the chemoreceptor trigger zone in the floor of the fourth ventricle.

In most investigations on antiemetic drugs, nausea is not mentioned, as it is not present in experimental animals and is apparently a psychic experience of man.[3] In our cases, of children who are severely retarded, the presence of nausea could not be established and the investigation of the effect of prochlorperazine had to be limited to that on emesis alone.

Material

A group of children in whom vomiting was of a chronic nature and a severe problem because of malnutrition and suspectibility to infections and debilitating conditions was selected. All of the children fitted into the group called "None" under classification of results. Patients taking anticonvulsive therapy or with cardiac, liver, or kidney

TABLE 1.—*Group 1*

Case No.	Age, Yr.	Diagnosis: Physical	Diagnosis: Clinical	Mental Status	Efficacy During Treatment Period	Remarks	Follow-Up Results
1	2		Mongolism	Moron	Slight		Slight
2	2		Mongolism	Imbecile	Slight		Slight
3	6		Mongolism	Imbecile	None		Excellent
4	7	Cerebral palsy	Birth trauma	Idiot	Good	Died; acute heart failure	
7	2		Mongolism	Imbecile	None		None
8	2		Mongolism	Moron	None		None
9	7		Mongolism	Imbecile	Excellent		Good
10	8		Mongolism	Imbecile	None		Slight

TABLE 2.—*Group 2*

Case No.	Age, Yr.	Diagnosis: Physical	Diagnosis: Clinical	Mental Status	Efficacy During Treatment Period	Remarks	Follow-Up Results
11	1	Hydrocephaly	Cranial anomaly	Moron	Excellent		Excellent
12	2		Epilepsy	Imbecile	Excellent		Fair
13	3	Cerebral palsy	Birth trauma	Imbecile	Slight		Fair
14	4	Cerebral palsy	CCSIP	Idiot	Excellent	Died	
15	4	Cerebral palsy	Infection	Idiot	None		None
16	5		Undiff.	Idiot	None	Died	
17	6	Quadriplegia	CCSIP	Idiot	None	Convulsions after drug was discontinued	Good
18	6	Cerebral palsy	Birth trauma	Idiot	None		Good
19	7	Micro-cephaly	Cranial anomaly	Imbecile	None	Nephritis	Slight
20	9	Cerebral palsy	CCSIP	Imbecile	None		None

TABLE 3.—*Group 3*

Case No.	Age, Yr.	Diagnosis: Physical	Diagnosis: Clinical	Mental Status	Efficacy During Treatment Period	Remarks	Follow-Up Results at 3 Mo
5	5	Epilepsy	Undiff.	Borderline	None		None
6	6	Epilepsy	Undiff.	Idiot	Excellent		Good
21	3		Undiff.	Idiot	Excellent		Excellent
22	4		Undiff.	Idiot	Good		Fair
23	9		Famil.	Imbecile	Slight		Slight
24	2		Mongolism	Imbecile	Good		Good
25	3	Cerebral palsy	Birth trauma	Imbecile	None		Fair
26	6		Undiff.	Idiot	Excellent	Drooler (imp.)	Good
27	7		Mongolism	Idiot	Excellent		Good
28	8	Cerebral palsy	CCSIP	Idiot	Fair		Excellent
29	8		Undiff.	Idiot	Excellent		Excellent
30	10		Undiff.	Idiot	Fair		Slight
31	4	Hyper-telorism	Cranial anomaly	Idiot	Fair		Slight
32	8		Undiff.	Idiot	Fair	Drooler (imp.)	
33	1	Cerebral palsy	Birth trauma	Imbecile	Good		Slight
34	8		Undiff.	Idiot	None		Excellent
35	7	Cerebral palsy	Kernicterus	Idiot	Good		Fair

conditions were excluded. There were 35 patients in all, and these were divided into three groups: Group 1, consisting of 8 patients in whom the vomiting was associated with subacute or chronic infection of the gastrointestinal or respiratory tract; Group 2, comprising 10 children in whom there was associated central nervous system disease; Group 3, consisting of 14 children who were habitual suckers of hands or tongue or in whom there were psychic causes such as severe anxiety. The accompanying Tables show the distribution of the patients in the different groups.

Method

The recommended dose of prochlorperazine was 0.25 mg. per pound of body weight, divided into

three equal daily doses.* Each child was started If side-reactions occurred, the medication was reduced or discontinued. A record card was kept for each child on which the daily dosage per pound, the total daily amount, and the duration were noted. Undesirable side-effects and laboratory data were also noted.

Results

Results were classified as follows: excellent, patient was completely free of vomiting; good, vomiting occurred not more than two or three times weekly; fair, daily vomiting of one whole meal or two or three small amounts of food; slight, daily vomiting of two full means and several small amounts at other times during the day; none, daily vomiting of at least three meals and several times in between.

In the following cases there were unusual results.

CASE 17.—The patient, aged 6, had a history of occasional convulsive seizures in infancy, but had been free of convulsions for three years and had not been on any anticonvulsant therapy for two years. This child experienced a moderately severe grand mal seizure 15 hours after prochlorperazine was discontinued. The child had been started on 7.5 mg., which dose was gradually increased to 12 mg. daily, at which point the response was considered fair. Convulsive seizures following discontinuation of therapy with prochlorperazine have not been previously recorded. It may have been purely coincidental in this case.

CASE 4.—The patient, aged 7, had lower spastic paralysis following a birth injury. On the second day of treatment, while receiving 8.7 mg. of prochlorperazine, the child vomited profusely and showed small petechiae over the body. Prochlorperazine was discontinued. The symptoms disappeared. Three weeks later the child developed severe vomiting and prochlorperazine was again given, this time 5.8 mg. daily (0.18 mg. per pound). The child responded well, remaining free of emesis during the following 15 days. The drug was then discontinued. Forty-eight hours after the drug was discontinued the child developed acute heart failure, and he died after two days. Autopsy confirmed the clinical diagnosis. Hypertensive conditions and cardiovascular collapse have occurred under treatment with phenothiazines, but they have also occurred in severely retarded children without such medication. In our case, the child received 0.18 mg. of prochlorperazine per pound of body weight, making a total of 5.8 mg. per day, and the first evidence of cardiovascular symptoms did not appear while the patient was receiving medication. They started 48 hours after discontinuation of the drug. It is not considered that the death was related to the use of prochlorperazine.

CASE 19.—The patient, aged 7, weighed 30 lb. Blood, liver, and urine findings before the drug was used were normal. After eight days of taking 7.5 mg. with no clinical response, the patient developed acute nephritis. The drug was discontinued. Recovery was considered complete after four weeks. Because vomiting had continued, the patient was again given 7.5 mg. of the drug, gradually increasing to 15 mg. per day. Treatment continued for 30 days. No pathological urine findings and no response to the drug occurred. No other side-effects were noted.

Table 4 shows the summary of results in the various groups.

Comment

If we include the three classifications, excellent, good, and fair, as a response to medication, 25% of the children in Group 1, 30% of the children in Group 2, and 75% of the children in Group 3 showed improvement during and following medication. If all three groups are combined, the response is 51%. These results are lower than have been reported previously,[6,7] where figures as high as 92% and 87% were reported. Smith,

* A solution of prochlorperazine ethandisulfonate containing 5 mg. per 100 drops was provided by Smith, Kline & French Laboratories, Philadelphia. on this dosage. If there was no effect at the end of one week, the dose was increased gradually until a change in condition resulted. If the child responded to the minimum dose, this was decreased gradually after one week, so as to establish the smallest amount which would cause improvement.

TABLE 4.—*Summary of Results*

Group	Efficacy During Treatment					Follow-Up at 3 Mo.				
	Excellent	Good	Fair	Slight	None	Excellent	Good	Fair	Slight	None
1	1	1	0	2	5	1	1	0	3	2
2	5	4	4	1	3	4	5	3	4	1
3	3	0	0	1	6	1	2	2	1	2

Kline & French Laboratories gave figures of 68.8% in 1166 cases.

There is a significant difference in results between Groups 1 and 2, on the one hand, and Group 3. The results in Groups 1 and 2 are very similar and rather poor. However, in Group 3, where it was felt that neurotic or behavioral patterns were probably responsible for the excessive vomiting, the improvement was 75%. It is possible that prochlorperazine had not only an antiemetic response but a tranquilizing effect as well, which might account for the better results in this group.

Two children in Group 3 were chronic droolers. In one of these (Case 26) drooling ceased completely after several days of therapy, while the other (Case 32) showed a temporary response but soon relapsed. Because of this, prochlorperazine was tried for eight profuse droolers. These patients were 1 to 9 years old and were treated with 0.2 mg. increasing to 0.77 mg. per pound of body weight, which amounted to 5 to 15 mg. per day. Not one of these children responded.

In the majority of cases the dose of drug used was three or four times higher than that recommended by the manufacturer. Doses as high as 0.93 mg. per pound of body weight daily were used, but the mean effective dose was approximately 0.25 mg. per pound.

It will be noted from the Tables that after three months without therapy only a few patients had shown any marked change in their vomiting status. In these few, some had shifted one classification to the right or to the left.

Conclusion

The small number of children investigated and their abnormal mental, physical, and neurological states do not permit conclusive assessment of this compound as an antiemetic in all children. It would appear, however, that the drug is a fairly effective antiemetic in vomiting associated with psychic phenomena. The reported incidents occurring after discontinuation of the drug are not considered as representing withdrawal complications.

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Mammalian Bites of Children

A Problem in Accident Prevention

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The pet population has been increasing rapidly, and in 1956 there were probably 25,000,000 dogs and 35,000,000 cats in this country.[1] Rabbits, squirrels, hamsters, and rats are also kept in great numbers by children. As pets around the home, only ponies and horses have decreased in number in recent years. The biting of children by pets is a common, although rarely fatal, accident. My associates and I submitted a questionnaire to 300 parents of 617 children coming under our observation for routine pediatric care. Among the 531 children in this survey who were over one year of age, 15.4% had, at some time, been bitten by a mammal, 2.1% of them more than once. Many of the bites were not considered severe enough to be reported to a physician.

TABLE 1.—*Mammalian Bites Reported in Twenty-Month Period*

Animal	Children, No.
Dog	132
Cat	7
Rabbit	3
Squirrel	4
Horse	5
Rat	2
Hamster	1
Monkey	1
Skunk	1
Raccoon	1
Total	157

The mammalian bites sustained by children in our pediatric practice, and reported to us, were investigated in detail over a 20-month period. They constitute the basis for this report.

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TABLE 2.—*Ages of Children Bitten by Mammals Over a Twenty-Month Period*

Ages, Yr.	Children, No.
0- 1	1
1- 2	5
2- 4	37
4- 6	32
6- 8	26
8-10	25
10-12	17
12-15	14
Total	157

Mammalian Bites

As shown in Table 1, there were 157 children bitten by mammals in the 20-month period. The average was 7.8 bites per month. Ninety-five of the children were boys, and 62 were girls. The ratio of three males to two females may be accounted for by the fact that boys are more aggressive in their relations with animals than are girls. The ages of this group are shown in Table 2. It is noteworthy that most of the children bitten were between the ages of 2 and 10 years. These are the years during which parental protection wanes, and adventurous and sometimes daring behavior takes place among children. For those under 2 years of age, protection is at its height and bites are few. After 10 years of age children have attained considerable discretion in handling animals and there is a decrease in the number of bites.

In this series there was little seasonal variation of bites. Usually, when children are indoors their pets are also. No less than 4 nor more than 15 bites were recorded in any one month.

The location of mammalian bites of children, as shown in Table 3, is significant because of the danger of rabies following a short incubation period when one is bitten

TABLE 3.—*Location of Mammalian Bites Sustained by Children over a Twenty-Month Period*

Location	Children, No.
Head	50
Upper extremities	58
Trunk	11
Lower extremities	38
Total	157

on the head by an animal harboring this virus. Only one of the children was bitten in the traditional location, the buttocks. That bites in this location are frequent is a myth.

Treatment

More than half of the children in this series were not examined; their parents were given advice on first aid over the telephone. Soap and water only were recommended for local care. Despite the fact that for several days after the accident a concentration of rabies virus may be found at the site of a bite inflicted by a rabid animal, viropexis probably takes place in a very brief period of time, possibly in five minutes. All local care, therefore, short of cauterization or destruction of tissue, no matter what agent is used, is probably useless after the first few minutes following the introduction of the virus into the wound.

If it is probable that the attacking animal is rabid and more than five minutes has elapsed before the wound is cleansed, or if the bite is too deep to irrigate with soap and water, cauterization with fuming nitric acid may rationally be used. In the 1957 Report of the Committee on the Control of Infectious Diseases of the American Academy of Pediatrics,[2] it is suggested that in wounds too deep to be adequately cleansed with a solution of soap or detergent, "a strong mineral acid such as nitric acid might be instilled into the depths of the wound." Koprowski [3] observed that all bite wounds, including skin abrasions exposed to licks of animals, should be cleansed immediately with soap or detergent solutions and added that benzalkonium (Zephiran) chloride in a 1% solution had proved effective in laboratory animals. He advised that puncture wounds not easily reached by these agents "may be treated with strong mineral acids." It is, however, not established that cauterization is advantageous. Rabies is such a rare disease in civilized countries that it is unlikely that a controlled study which might answer the problem will be conducted. Reports of animal experimentation are lacking. The recent knowledge that viropexis takes place relatively quickly after human tissue is infected with rabies virus gives credence to the time-honored practice of cauterization of some animal bites.

Traditionally, animal bites are not sutured, presumably because all such wounds are contaminated by bacteria. The practice of leaving these wounds open is commonly recommended in textbooks on surgery. Nevertheless, in some instances when the wounds may cause disfiguring scars and when there is no probability of the animal harboring rabies, dog bites may be sutured with impunity with use of sterile technique after thorough cleansing of the wound. In several of my cases of bites of the face the lesions were sutured, and healing took place promptly by first intention. Bite wounds elsewhere were left open, in accordance with the accepted practice.

The problem of tetanus control was considered in every case in the series, and booster doses of toxoid or serum were administered when indicated. None of the children were bitten by an animal proved to be rabid. Thirty-one children, however, received five or more injections of rabies vaccine, and three received rabies serum. The recommendations of the World Health Organization Expert Committee on Rabies (Table 4) were used as a guide, with exceptions being made in some cases on the basis of the health of the animal involved in the accident, its almost certain immunity to rabies, and its limited opportunity for contact with rabies virus because of a cloistered life.

Rabies in this country is a rare disease in humans (Table 5), and in some states

TABLE 4.—*Indications for Specific Postexposure Treatment* *

Nature of Exposure	Condition of Biting Animal		Recommended Treatment
	At Time of Exposure	During Observation Period of 10 Days	
I. No lesions; indirect contact only	Rabid	----	None †
II. Licks:			
(1) Unabraded skin	Rabid	----	None †
(2) Abraded skin and abraded or unabraded mucosa	(*a*) Healthy	Healthy	None
	(*b*) Healthy	Clinical signs of rabies or proven rabid	Start vaccine at first signs of rabies in animal (or laboratory diagnosis)
	(*c*) Signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on 5th day after exposure ‡
	(*d*) Rabid, escaped, killed, or unknown	----	Start vaccine immediately
III. Bites:			
(1) Simple exposure	(*a*) Healthy	Healthy	None
	(*b*) Healthy	Clinical signs of rabies or proven rabid	Start vaccine at first signs of rabies in animal
	(*c*) Signs suggestive of rabies	Healthy	Start vaccine immediately; stop treatment if animal is normal on 5th day after exposure ‡
	(*d*) Rabid, escaped, killed, or unknown; or any bite by wolf, jackal, fox, or other wild animal	----	Start vaccine immediately
(2) Severe exposure (multiple or face, head, or neck bites)	(*a*) Healthy	Healthy	Hyperimmune serum immediately; no vaccine as long as animal remains normal
	(*b*) Healthy	Clinical signs of rabies or proven rabid	Hyperimmune serum immediately; start vaccine at first sign of rabies (or laboratory diagnosis)
	(*c*) Signs suggestive of rabies	Healthy	Hyperimmune serum immediately followed by vaccine; vaccine may be stopped if animal is normal on 5th day after exposure
	(*d*) Rabid, escaped, killed, or unknown; any bite by wild animal	----	Hyperimmune serum immediately, followed by vaccine

* Prepared from World Health Organization Technical Report No. 82, page 12.
† Start vaccine immediately in young children and in patients where a reliable history cannot be obtained.
‡ An alternative treatment would be to give hyperimmune serum and not start vaccine as long as the animal remained normal. To be effective, hyperimmune serum must be given within 72 hours of exposure. Dose: 0.5 ml. per kilogram of body weight. These indications apply equally well whether or not the biting animal has been previously vaccinated.

it has not been discovered in animals for many years. There is no doubt, however, that there is a great reservoir of this virus in nature, probably all over the world, and it is found with increasing frequency among wild mammals when search for it is made. The discovery of rabid bats in 15 states [4] means that, in theory at least, no place, not even a city, is safe from this virus, which in effect may become air-borne when transported by a bat.

Reports from individual veterinary practitioners that there is no rabies in the community may give the physician a false sense of security. Only rabies control centers such as are maintained by some State Boards of Health may be expected to have reliable information. The parents of one of my patients who had received a dog bite were told by a veterinarian with a large practice that no rabies had been discovered in the area in a year or more. As a matter of fact, three rabid animals, a dog, a raccoon, and a bat, had recently been found by the Board of Health in the county in which the child lived.

The decision to withhold the administration of vaccine or serum when a situation exists that calls for either, as recommended by the World Health Organization Expert Committee on Rabies, is a difficult and even dangerous one for physicians. Exceptions may be made, but with caution. Administration of the protective agent is not without danger. The incidence of neuroparalytic accidents after the administration of purified

TABLE 5.—*U. S. Death Rates for Rabies*

Year	Fatalities, No.	Year	Fatalities, No.
1937	59	1947	26
1938	66	1948	34
1939	40	1949	10
1940	41	1950	18
1941	39	1951	18
1942	36	1952	24
1943	47	1953	12
1944	56	1954	13
1945	43	1955	6
1946	34	1956	9

rabies vaccine propagated in rabbit neurological tissues, as reported in the past 10 years, varies from 1 in 527 patients to 1 in 7200 patients.[5-8] Steele,[9] considering published and unpublished data accumulated by the veterinary branch of the United States Public Health Service, estimated that accidents occur once in approximately 1500 patients. Fatalities have been reported following the administration of conventional rabies therapy. Antirabies serum, which has had limited use, is a relatively crude horse serum,[10] and, even after skin testing, severe reactions are known to occur. One is, then, faced with the necessity of weighing the remote danger of a fatal disease against the administration of a potentially harmful and painful series of injections. In the case of head bites, I have withheld the administration of vaccine and serum in some instances when the animal was known to have been immunized recently against rabies, when a puppy with little or no possibility of exposure to rabies was involved, or when a dog that had been house-confined was involved, there having been no known rabies in the community in recent months. I frequently call veterinarians concerning a dog's immunization record, as owners may confuse the injections given for protection from distemper and from rabies. The management of the animal, the victim, and the bite itself, when a problem of rabies control exists, has been extensively discussed recently by Habel.[11] His paper should be of great value, especially when unusual situations arise.

Duck-embryo rabies vaccine, with which I have had limited personal experience, may entirely replace the conventional vaccine prepared in neurological tissue of rabbits. It is undergoing extensive field trial by the World Health Organization. Early experience with the vaccine, reported by Peck, Powell, and Culbertson,[12,13] was encouraging. According to Peck,[14] in 17 of 205 bite cases at one hospital in which the vaccine was given the vector proved to be rabid, but no rabies resulted in any of the cases. In only two cases were there systemic reactions; neither was serious, and one may have been due to tetanus antitoxin or penicillin administered at the time the rabies vaccine series was started, rather than to the vaccine itself. Local reactions after use of the duck-embryo rabies vaccine are probably no severer than those associated with the vaccine prepared from rabbit neurological tissue. It was Peck's impression that they are less severe.

Why Do Animals Bite Children?

Quipsters prate that there are three American institutions above criticism—Motherhood, the United States Marines, and Dogs. We wish we could be the child's advocate rather than the dog's in the problem of bites, but, by a great majority in our series, the child, not the animal, was at fault. The following case histories are typical.

A boy, aged 4, kicked the neighbor's dog lying under the car. The dog bit his leg.

A boy, aged 11, made a dirt tunnel over a neighbor's dog and then stuck his hand into the tunnel. The dog nipped his hand.

A boy, aged 4, picked up his dog and squeezed it as hard as he could. The dog nipped him on the eyebrow.

Several children in this series were bitten by dogs while trying to quell a fight between animals.

A girl, aged 10, was severely bitten on the knees by an unknown dog when trying to protect her dog in a dog fight.

There were several instances in which the "bite" was not a bite at all, but instead a puncture wound.

A boy, aged 5, was playing with one of his dogs on the floor, rolling a ball in front of the dog's nose. The boy's other dog made a lunge for the ball, but struck the boy's cheek instead, leaving several puncture wounds, obviously not made by opposing teeth.

Since jumping, lunging, excited dogs play with their mouths open, it is to be expected that human skin may sometimes come in contact with their teeth, especially when the human involved in this type of accident is a small child with slow reflexes. Usually, the dogs involved in accidents of this kind

in our series were immature. Puppies may also bite in play and were more of a hazard than mature dogs in our cases.

In still another group, the children were bitten on the ankles or legs while riding bicycles. In cases of this type, it seems that the offending dogs are more excited by turning wheels than ankle or leg, but while on the run they find the latter easier to bite.

There were also several examples of children being bitten when exploring or wandering. In these cases, the dogs involved appeared to be protecting their own houses.

A new boy in the neighborhood, aged 5, walked through a neighbor's back yard and was bitten on the leg by an old dog belonging to the neighbor.

It is true that a few dogs are aggressive and are repeated offenders, such as the dog which attempts to bite all delivery men, including the postman. These dogs rarely attack away from their own grounds, but, even so, they may have to be eliminated. Only one child was bitten by a mother of a new litter of puppies, the child being unknown to the mother dog. None of the children was believed to have been bitten by dogs in heat; however, this may have been possible when unknown dogs were involved. Dogs in heat, supposedly highly excitable, certainly do not attack children within the home with any great frequency. While it is hazardous to give a motive to an animal, observation would indicate that dogs bite humans (1) in self-defense; (2) during play, unintentionally; (3) in protection of their own property, and (4), rarely, with aggression and savagery.

In this series cats, too, seem to be almost blameless in biting children, as the following histories illustrate.

A girl, aged 4, was holding her cat on her shoulder. It wanted to get down, but, rather than let go, she pulled its tail. The cat bit the child on the shoulder.

A boy, aged 3, hit at his cat with a belt, and the cat bit his arm.

A girl, aged 10, went to a neighbor's yard to rescue kittens from a dog, one of which was in the dog's mouth. She rescued the dying kitten from the dog, but it bit her on the hand.

The four squirrel bites were most troublesome, as all of the squirrels were wild and either died or escaped. Two of the squirrels were sick or injured at the time they bit the children. One child was bitten on the finger while feeding an apparently healthy squirrel in a park. The other healthy squirrel was knocked out of a tree and caught by an agile lad who also sustained a finger bite.

The five horse bites in this series were unexpected, as riding is not a popular sport among our patients. All of the horses were family-owned, and in four of the five instances the biting seemed to be deliberate.

A girl, aged 5, was passing the horse's stall. It playfully reached out and nipped her on the shoulder.

A boy, aged 10, was getting into the saddle when the horse bit him painfully on the leg.

One of the bites appeared to be accidental.

A boy, aged 4, was feeding the horse a piece of candy through the fence. The horse nibbled his finger.

The three biting rabbits were all owned by their child victims, whose fingers were bitten while the animals were being fed or teased.

The experiences of the children bitten by rats were as follows:

A girl, aged 11, saw two cats fighting over what she thought was a ground hog. In attempting to rescue the victim, she was bitten on the finger by a large rat, which made its escape. She received a full course of rabies vaccine.

A girl, aged 11, was bitten by a white rat being raised by the children in her classroom. She did not receive prophylactic injections. The animal was observed.

All of the children bitten by the more unusual animals—monkey, skunk, raccoon, and hamster—were involved with pets, and, as none of the bites were on the head, the animals were observed.

Should Children Keep Mammals as Pets?

The joy that millions of children receive from pets, particularly dogs, far outweighs the danger incurred from bites and disease that the animals may inflict on them. The proper care of animals teaches a respect for living creatures. This emotionally healthy attitude prevents the acquisition of an un-

reasonable fear of animals, often neurotic, that many children carry into adult life. When a child acquires a pet, his parents must assume new responsibilities in training and discipline. The following rules will help to prevent the common accident of bites from animals.

1. Children should not own pets until they can care for them and show discretion in their handling. Such ability is rare under the age of 4 years and unusual under the age of 6 years.

2. Usually, older animals are to be preferred to immature ones as pets for young children.

3. Children should be taught that animals have rights, including an existence free of pain and excessive teasing.

4. In the early years, children should be taught to avoid all strange animals, especially sick or injured ones. This precaution does not mean that a fear of dogs, cats, and other domestic animals should be created.

5. Even as toddlers, children should be taught not to trespass, and as older children, when riding bicycles, they should deliberately avoid routes where dogs are known to chase vehicles.

6. Under the supervision of an adult, children should make friends with the pets in their immediate neighborhood.

7. Children should be instructed not to quell a fight between animals even though their own pet is involved. Instead, they should call for an adult, use a garden hose on the animals, or try to get their pet away from the melee by cajoling.

Summary

A survey of 617 children receiving routine private pediatric care disclosed that 15.4% of those over one year of age had been bitten by a mammal, 2.1% of them more than once. A series of 157 cases of mammalian bites sustained by children over a 20-month period is reported in which investigation of the age and sex incidence of the children and of the seasonal variation and location of the bites was made.

Treatment is discussed in some detail, with particular reference to the problems of tetanus control and administration of rabies vaccine or serum.

In this series the preponderance of evidence showed that usually the child was at fault in provoking the bite. Illustrative cases are cited. The dog was by far the most frequent offender; other animals involved were the cat, rabbit, squirrel, horse, rat, hamster, monkey, skunk, and raccoon.

Since the emotional and educational value of pets far outweighs the danger of bites and disease to which children are subjected from this source, seven rules are suggested to help prevent accidental biting of children by mammals. The relative frequency with which the children in this survey sustained this type of accident emphasizes the need for preventive measures.

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Studies in Sickle-Cell Anemia

XI. Bone Involvement Simulating Aseptic Necrosis

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Sickle-cell anemia (SCA) was first described in 1910,[1] but involvement of osseous tissue in this disease was not reported until 1924, when Graham [2] autopsied a 30-year-old man and found the marrow cavity reduced in size and at one point obliterated. In 1927, Cooley [3] described a skull which on roentgenography showed widening of the diploic spaces, a thin or absent outer table, and parallel lines radiating from the inner table. Similar roentgenograms have subsequently been reported in other patients with SCA.

More recently, there have been additional publications [4-32] on bone involvement in SCA, but few of these report aseptic necrosis of the femur or the humerus. This paper presents two additional cases of aseptic necrosis of the femur in children with SCA. One of these cases also showed aseptic necrosis of the head of the humerus.

Report of Cases

CASE 1.—A 14-year-old Negro boy was hospitalized on Sept. 21, 1955, complaining of pain in both hips, more severe on the left, of three months' duration. He had been admitted to another hospital in July, 1955, because of severe bilateral hip pain, inability to walk, and weight loss of three weeks' duration. Icteric sclerae and dark urine were noted on that admission. A film of the hip joints taken at this time (Fig. 1*A*) revealed slight demineralization of both femoral necks adjacent to the epiphyseal lines.

When he was admitted to this hospital, six weeks later, his mother stated that he had been diagnosed as having SCA at the age of 9 months and that he had been hospitalized on numerous occasions for crises, for which he had received many blood transfusions. A 12-year-old sibling and a maternal uncle also have SCA.

Physical examination revealed an asthenic, poorly developed child who appeared small for his age. He weighed 63 lb. and was 56 in. tall. The skull was tower-shaped. The heart was not enlarged, but a Grade 3 systolic murmur was present. The liver edge was 2 cm. below the right costal margin. The spleen was not palpable. There was generalized lymphadenopathy. Examination of the lower extremities showed a positive Trendelenberg sign on the left, with no shortening of either lower extremity. Movement of the hip joints caused severe pain. There was limitation of flexion, external rotation, abduction, and extension of the hip joints, more marked on the left. Pain was experienced on active abduction of the right shoulder, but movement was otherwise normal.

Laboratory Data.—Hemoglobin, 9.2 gm.; erythrocytes, 4,270,000; hematocrit value, 36%; leukocytes, 12,000 (59% polymorphonuclear cells, 20% small lymphocytes, 17% large lymphocytes, 2% monocytes, 2% eosinophils). There were a few target cells and also microcytosis, anisocytosis, and poikilocytosis. The reticulocyte count was 2.8%. The wet blood specimen showed 75% sickling (sodium metabisulfite method). Alkali-resistant hemoglobin after five minutes was 3.2%. Paper electrophoretic analysis revealed S-S hemoglobin. The total protein, albumin-globulin ratio, serum bilirubin (van den Bergh), cholesterol, alkaline phosphatase, calcium, and phosphorus determinations in the blood were within normal limits. The specific gravity of the urine was 1.012. The Kahn test was negative.

Roentgen Findings.—Examination of the hip joints on admission to the hospital demonstrated a progression in the degree of decalcification in the proximal ends of both femoral necks and beginning irregularity of the femoral capital epiphyses, associated with a spotty type of demineralization. At this time, a diagnosis of bilateral aseptic necrosis was made (Fig. 1*B*).

Films of both shoulders made at this time (Fig. 2) revealed spotty decalcification of the

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Fig. 1 (Case 1).—Roentgenograms of hip joints. *A*, slight demineralization of both femoral necks adjacent to epiphyseal lines (July, 1955). *B*, widening and irregularity of femoral capital epiphyses with areas of demineralization (September, 1955). *C*, bilateral "mushroom" deformity of femoral capital epiphysis (July, 1956).

right humeral capital epiphysis which resembled that noted in the femoral capital epiphyses. This alteration was also thought to be due to aseptic necrosis. The left shoulder was normal.

The patient was placed in leg traction for three months and then was allowed to be on crutches for the following six months. During the first 15 minutes of a swimming exercise, the patient developed severe pains in the lower extremities. The pains lasted approximately 36 hours and necessitated rehospitalization. Roentgen reexamination of the hips and right shoulder were made at this time. The hip joints (Fig. 1*C*) revealed slight fragmentation and marked flattening of the

Fig. 2.—Spotty decalcification of right humeral capital epiphysis (September, 1955).

capital epiphyses, producing a mushroom-like deformity. There was also some broadening of the femoral necks. Examination of the right shoulder showed irregular destruction of the medial margin of the humeral capital epiphysis and a similar destructive process involving the upper medial aspect of the humeral shaft adjacent to the epiphyseal line. After four days of moderate intermittent pain in both hips and knees, the patient became asymptomatic, and he was placed in traction for two and one-half months. He was discharged in a wheel chair. He was advised that his legs should be permitted no weight-bearing. Roentgenograms of both hip joints taken before discharge showed a slight to moderate degree of recalcification (healing) of all of the involved bony components.

On follow-up examination four months later, in March, 1957, the mineralization of both hip joints appeared to be normal. The femoral necks remained widened, and the femoral capital epiphyses were still enlarged and flattened, but the fragmentation had almost completely disappeared (Fig. 3). Repeat examination of the right shoulder also showed normal mineralization of the bones. The previously demonstrated area of destruction on the medial aspect of the humeral capital epiphysis was barely preceptible, and the articular surface in this region was smooth. At this time, examination of the patient showed more marked limitation in motion

Fig. 3.—Recalcification (healing) with enlargement and marked flattening of the femoral capital epiphyses and widening of the femoral necks (March, 1957).

Fig. 4 (Case 2).—Roentgenogram of both hips. Note shortening of left femoral neck with circumscribed area of bone destruction near epiphyseal line.

of both hip joints in all planes. No pain or limitation of motion was elicited in the right shoulder. He was advised to continue ambulation in a wheel chair until further healing could be demonstrated by roentgen examination.

Case 2.—A 14-year-old Negro boy had been diagnosed as having SCA at the age of 5 years. His crises were severe and usually began with unrelenting pain in the extremities and back, which resulted in 18 hospital admissions. On Feb. 13, 1952, there was an unusually severe attack of pain in the left lower extremity, with a residual inability to walk. Muscle testing showed weakness of the flexors, abductors, and extensors of the left hip. Neurological and electroencephalographic examinations revealed no abnormal findings. Roentgenogram of the pelvis and long bones taken during this episode showed no abnormality, but reexamination two months later revealed flattening and enlargement of the left femoral capital epiphysis, associated with punctate demineralization (Fig. 4). There was also widening and apparently slight shortening of the left femoral neck. In the proximal one-half of the neck adjacent to the inferior medial aspect of the epiphyseal line, a small area of bone destruction was seen. These changes were typical of aseptic necrosis.

The erythrocyte count ranged between 1,700,000 and 2,500,000, and the hemoglobin, between 4 and 8 gm. per 100 cc. Paper electrophoresis demonstrated S-S type of hemoglobin.

The most recent examination revealed a 2 cm. shortening of the left leg. His left shoulder was carried higher than the right. At the time of discharge he was free of pain but was advised to use crutches for ambulation.

Comment

The pathogenesis of aseptic necrosis as described in these cases may be related to the development of thrombosis in blood vessels supplying the affected bones. This type of involvement is more commonly seen in older children and adults. On the other hand, skeletal involvement in infants and young children is more likely to be expressed as hyperplasia of marrow, widening of marrow spaces, thinning of cortex, and osteoporosis (Fig. 5).

Thrombosis of these vessels may cause hemorrhage, necrosis, fibrosis, abnormal calcification, and new bone formation.[33] Chandler[34] stated that following experimental interruption of the blood supply to the femoral head the osteoblastic cells disappear from their position along the bone trabeculae and the marrow spaces became filled with a fine precipitate of necrotic material. The trabeculae are gradually absorbed and may collapse under the pressure of weight-bearing and muscle-pull. These reactions can be disseminated and

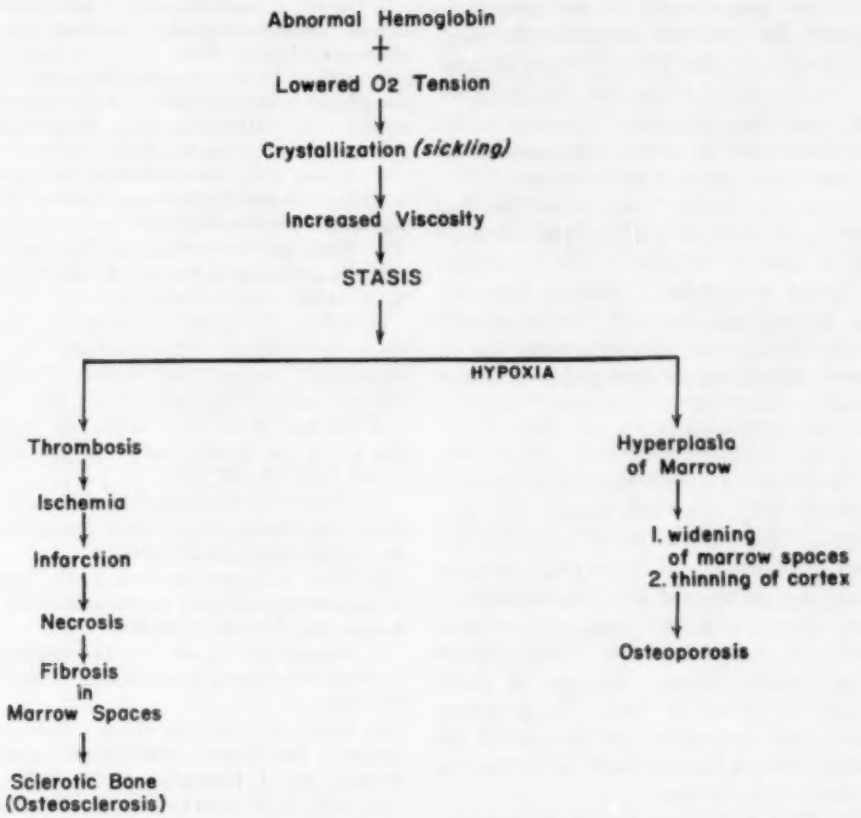

Fig. 5—Schematic representation of pathogenesis of osseous changes in sickle-cell anemia. (Adapted and modified from Vorder Bruegge and Diggs.[39])

appear as cysts (as seen in Case 2), or the area of necrosis may be massive and appear as a sequestrum. Dead bone exerts a reparative stimulus and causes invasion of the necrotic area and its replacement by new bone.[35,36] The more vascular the immediate environment the more rapid and complete is the repair.

Thrombosis of vessels supplying bone may produce an infarction and necrosis which would show as sclerosis on the roentgenogram. As vascularization removes the dead bone, the picture would show patchy areas of osteoporosity surrounded by denser bone. Finally, new bone is laid down. If the surface of the joint is involved, interference with function may result.

The osseous changes in our patients can be directly attributed to SCA. Clinical studies showed no evidence of any other metabolic, infectious, or endocrine disorder which could have produced necrosis of bone. The cases are similar to these described by Ehrenpreis and Schwinger,[37] Moseley and Manly,[38] and others.[18,19,28,32] Ehrenpreis reported that the necrosis of the humerus was repaired within one year, whereas in three cases involving the head of the femur there was no improvement. Moseley cited a patient aged 7 years and another aged 17 years in whom the head of the femur returned to normal. Another patient, aged 38, did not improve.

In our Case 1 there has been almost complete repair of the humeral lesion but only

very slow improvement in the mineralization of the involved areas in the hips. Follow-up of Case 2 was limited because the family moved to another area and contact was lost. However, it appears that ambulation will be permanently impaired in the two cases reported in this paper.

Smith and Conley[28] emphasized the fact that aseptic necrosis is a characteristic finding in genetic variants of SCA such as sickle-cell hemoglobin C disease. However, our findings and those of Tanaka et al.[40] clearly indicate that aseptic necrosis may be found in homozygous hemoglobin S disease also.

Summary

Two cases of aseptic necrosis of bone in children with sickle-cell anemia are presented. This osseous lesion probably follows thrombosis of the blood vessels supplying the affected area. Involvement of the femoral neck and head may produce pathology indistinguishable from classical Legg-Perthes disease. Therapy is based mainly on orthopedic care. The prognosis varies with the extent and the site of the lesion. Weight-bearing tends to increase the severity of the disease.

Dr. T. Wilkins Davis, Division of Radiology, supplied the roentgen interpretation.

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Characteristics of Heart Disease Seen in a Case-Finding Program

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Introduction

The purpose of this paper is to report the characteristics of heart disease observed in the course of a large-scale case-finding program for childhood heart disease in Colorado school children. A secondary purpose is the estimation of the accuracy of diagnosis resulting from a screening type of auscultatory examination of the heart in children. The methodology,[1] preliminary findings as to prevalence,[2] and the results of follow-up studies[3] have been reported. A paper dealing with the relationship of heart disease prevalance to population characteristics[4] is in preparation.

Two groups of children were included in the study. The "regular" sample was made up of 11,236 children enrolled in the sixth grade of schools in 41 of Colorado's 63 counties. This group of children represents a random sample of sixth graders. The "extra" sample was composed of 1705 children who did not fall into the regular sample but were examined because of suspicion of or previous diagnosis of rheumatic fever or heart disease or both. This latter sample was highly selected and nonrepresentative of the school population.

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Method

A diagnosis was recorded for each child examined. The diagnosis was arrived at by simple stethoscopic examination of the cardiovascular system. The examinations were done by teams of physicians with long experience in pediatric cardiology. A diagnosis of potential rheumatic heart disease was assigned only when the child had no evidence of heart disease but either appeared to be in the acute rheumatic state or gave a history of rheumatic state, in the past, which was so clear-cut that there was no question in the minds of the examiners. Of the total 10,990 children in the regular sample who showed no evidence of heart disease at the time of the study, 5.3% had a reported diagnosis of the acute rheumatic state in the past but only about 0.9% of the total were designated as having potential rheumatic heart disease for purposes of this study.

A diagnosis of definite heart disease was assigned only upon full agreement of two examiners. If either examiner had any doubts, a diagnosis of suspected heart disease was recorded.

The criteria of diagnosis were those recommended by the American Heart Association[5] as they apply to findings on physical examination without laboratory or other diagnostic aids, largely on auscultatory findings. These criteria were applied conservatively, especially with regard to systolic murmurs in the apical area. Unless such a murmur was high-pitched, transmitted to the axilla, and accentuated by exercise and shift of the patient to the left lateral position, it was not labeled as definite mitral insufficiency. In the auscultatory differentiation of physiologic murmurs from murmurs of congenital heart disease, especially those that occur at the base or along the left sternal border, we generally regarded as physiologic those that were medium-pitched, rather vibratory, and showed change in quality with respiration and change in position. There was a

further element of conservatism in that the examiners, because of their experience,, tended to be more concerned about the dangers of overdiagnosis than of underdiagnosis of heart disease.

Findings

The distribution of diagnoses, after removal of those persons for whom some major characteristic was unknown or not specified, is shown in Table 1. The apparent discrepancies between these figures and those previously reported [1,2] are due to the exclusions mentioned above and a few revisions of diagnosis after review of the case.

The distribution of diagnoses within each sample is what is to be expected from the difference in the nature of the samples. Although the prevalence of definite heart disease is seven times greater in the extra subjects than in the regular sample, the distribution of etiologic types of definite heart disease is the same in both groups of examinees.

Because of the frequency with which innocuous murmurs occur in children and because of the fact that the evaluation of murmurs is the principal problem in the diagnosis of childhood heart disease, our observations may be of some interest. Of the total children in the regular sample (mean age, 12 years), 36.5% had physiologic murmurs as the only findings. It appeared that the proportion of children with such murmurs decreased slightly with increase in age. Females had such murmurs somewhat more frequently than males, and Spanish Americans had them somewhat less frequently than Anglo-Americans, but these differences are probably accounted for by differences of age.

Physiologic murmurs were recorded as to the precordial area where best heard and divided into five categories. Those designated as "base" were heard best at the pulmonic or aortic areas, with the former predominating; those designated as "left sternal border" were heard best in the third, fourth, or fifth interspaces at the left border of the sternum, while murmurs heard diffusely and not well localized were designated as "most of the precordium." Apical and "other" sites made up the remainder. Left sternal border murmurs made up 73% and basal murmurs made up 18% of the total. There were no appreciable differences in the site of maximum intensity as related to age, sex, or race, in the regular sample.

Given our conservative criteria for the diagnosis of potential rheumatic heart disease, it is found that none of the 96 regular subjects were so diagnosed because of active rheumatic state at the time of examination. Of the 80 extra subjects diagnosed as having potential rheumatic heart disease, 7, or 8.8%, had clinically manifest active rheumatic state (6 with active polyarthritis, 1 with active chorea) at the study examination. The majority, then, were diagnosed on the basis of a clear-cut history of the rheumatic state at some time prior to the study.

The proportion of the total children examined in the regular sample who were thought to have the active rheumatic state was surprisingly low. The diagnosis of activity of the disease process had to be

TABLE 1.—*Distribution of Study Diagnoses by Sample*

Study Diagnosis	Regular Sample		Extra Sample	
	No.	Per Cent	No.	Per Cent
No heart disease	6,820	61.12	926	54.40
Physiologic murmur only	4,074	36.52	556	32.67
Potential rheumatic heart disease	96	0.86	80	4.70
Suspected heart disease (all types)	60	0.54	26	1.53
Definite heart disease	107	0.96	114	6.70
RHD	75	0.67	82	4.82
CHD	30	0.27	29	1.70
RHD and CHD	1	0.01	2	0.12
Other	1	0.01	1	0.06
Total diagnoses	11,157	100.00	1,702	100.00

TABLE 2.—*Number of Cases with Active Rheumatic State and Rate per 1,000 Examinees*

Clinical Manifestation of Active Rheumatic State	Regular Sample		Extra Sample	
	No.	Rate per 1,000 Examinees	No.	Rate per 1,000 Examinees
Polyarthritis	0	0.0	6	3.5
Chorea	0	0.0	1	0.6
Carditis	7	0.6	16	9.4
Definite	2	0.2	4	2.3
Suspected	5	0.4	12	7.1
	7	0.6	23	13.5

made on clinical evidence without laboratory aids. It was made conservatively. Every effort was made to examine every sixth grader in the regular sample who was not in school at the time of the study examination but suspected of being out of school because of an acute illness which might be active rheumatic state. We do not feel that the observed rates for active rheumatic state are low to any significant degree as a result of missing those homebound by active disease. Table 2 gives the data.

It will be seen from Table 2 that only two of the regular sample had clinically definite active rheumatic carditis. These two cases were included in the diagnostic group of definite rheumatic heart disease, so that, of the latter, 2.6% also had definitely active carditis. For the extra group, the corresponding proportion was 4 out of 84, or 4.8%. None of the persons shown in Table 2 had more than one manifestation of the active rheumatic state at the time of examination.

There were 211 children in whom a diagnosis of rheumatic heart disease was seriously considered at the time of this study. They are shown in Table 3 in relation to the degree of certainty of diagnosis.

Table 3 indicates that of the total 211 subjects in both groups, 160, or 76%, could be labeled as having definite rheumatic heart disease. Of those with definite heart disease, the proportionate distributions of lesions in the regular and extra groups are remarkably similar. The group with suspected heart disease points up the fact that a major diagnostic problem is the differentiation of mitral insufficiency from apical area systolic physiologic murmurs.

The relationship of definite rheumatic heart disease found in the study to earlier diagnosis of the acute rheumatic state or heart disease is shown in Table 4.

Some caution must be used in interpreting Table 4. The data represent responses to inquiries to a simple questionnaire submitted to the parents of each child. The answers represent the parents' knowledge of diag-

TABLE 3.—*Cases of Rheumatic Heart Disease Distributed by Certainty of Diagnosis, by Sample, and by Valvular Lesion*

Valvular Lesion *	Definite RHD		Suspected RHD	
	Regulars	Extras	Regulars	Extras
Combination of valvular lesions				
M. I. alone	40	46	31	12
M. S. alone	4	1	0	1
A. I. alone	4	5	0	1
M. I. + M. S.	18	19	0	1
M. I. + A. I.	3	1	0	1
M. S. + A. I.	1	1	0	0
M. I. + M. S. + A. I.	6	11	0	0
Not specified	0	0	3	1
Total cases	76	84	34	17
Individual valvular lesions				
M. I.	67	77	31	14
M. S.	29	32	0	2
A. I.	14	18	0	2
Not specified	0	0	3	1
Total lesions	110	127	34	19

* M. I., mitral insufficiency; M. S., mitral stenosis; A. I., aortic insufficiency.

TABLE 4.—*Answers to Questions Relative to Previous Diagnosis of the Acute Rheumatic State or of Heart Disease in Definite Rheumatic Heart Disease Cases, Both Samples*

Previous Diagnosis of Acute Rheumatic State	Previous Diagnosis of Heart Disease			Total
	Not Stated	Answer is "No"	Answer is "Yes"	
Not stated	49	0	0	49
Answer is "no"	0	1	14	15
Answer is "yes"	1	30	65	96
Total	50	31	79	160

noses which may have been made at an earlier date. When no statement is made in response to the question, there are no grounds for rigorous interpretation. However, making the assumption that the "not stated" categories indicate no knowledge on the parents' part that the child had ever had the diagnosis in question, it appears that about 40% of those with definite heart disease had previous diagnoses of both the acute rheumatic state and heart disease. Those with a previous diagnosis of the acute rheumatic state made up only 19% of the total, and those with an earlier diagnosis of heart disease alone were about 9% of the total 160 cases.

In comparing the regular and extra groups as to previous diagnoses it can be shown that 50% of the "extra" sample cases of definite rheumatic heart disease had had both diagnosis of the acute rheumatic state and of heart disease. The corresponding figure for the regular group was 30%, a difference to be expected because of the different nature of the two samples.

These data are, at best, crude, and their interpretation must be judged in the light of the method of collection of data and the assumptions made.

There were a total of 112 children for whom a diagnosis of congenital heart disease was considered. We were fully aware of the pitfalls in attempting diagnosis of specific lesions of congenital heart disease without detailed study of the individual case. However, in the interest of determining the relative accuracy of diagnosis as based on simple cardiac examination in the field, the most likely specific lesion of congenital heart disease was recorded (Table 5).

Table 5 indicates that, in the field, diagnosis of congenital heart disease is attended by more uncertainty than the diagnosis of rheumatic heart disease.

Study was made of those with definite congenital heart disease as to diagnosis of rheumatic state or heart disease or both prior to this investigation. This point is considered because of frequency with which the presence of a murmur of congenital heart disease is erroneously interpreted as evidence supporting a diagnosis of the acute rheumatic state or of rheumatic heart disease or both. The relevant data are given in Table 6.

TABLE 5.—*Cases of Congenital Heart Disease Distributed by Certainty of Diagnosis, by Sample, and by Most Likely Specific Lesion*

Most Likely Lesion	Regular Sample		Extra Sample	
	Definite H. D.	Suspected H. D.	Definite H. D.	Suspected H. D.
Auricular septal defect	7	3	7	7
Ventricular septal defect	11	14	4	8
Patent ductus	5	1	5	1
Coarctation of the aorta	5	4	4	1
Tetralogy of Fallot	0	0	3	0
Other lesions	3	10	7	0
Dextrocardia	0	0	1	1
Total	31	32	31	18

Table 6 is set up in the same fashion as Table 4. With equal reservation as to the reliability of the data and by making the same assumption, it can be seen that 33 of 62, or 53%, had a previous diagnosis of heart disease. However, 7 of these 33 had a diagnosis of rheumatic rather than congenital heart disease. Only 9, or 14%, of the 62 had an earlier diagnosis of the acute rheumatic state. This contrasts sharply with the 160 cases of definite rheumatic heart disease, 60% of whom had a prior diagnosis of the acute rheumatic state.

Comparison of the regular with the extra group shows about the same pattern with regard to previous diagnoses except that

TABLE 6.—*Answers to Questions Relative to Previous Diagnosis of the Acute Rheumatic State or of Heart Disease in Definite Congenital Heart Disease Cases, Both Samples*

Previous Diagnosis of Acute Rheumatic State	Previous Diagnosis of Heart Disease			Total
	Not Stated	Answer is "No"	Answer is "Yes"	
Not stated	23	0	0	23
Answer is "no"	0	4	26(3)	30
Answer is "yes"	0	2	7(4)	9
Total	23	6	33(7)	62

* Figures in parenthesis are the number of such cases in which the answer specified that rheumatic heart disease had been diagnosed.

TABLE 7.—*Comparison of Screening Diagnosis with Diagnosis Resulting from Detailed Clinical Follow-Up Within a Two-Year Interval*

Screening Diagnosis	Diagnosis at Time of Follow-Up						Total
	No Heart Disease	Definite Heart Disease			Suspected Heart Disease		
		RHD	CHD	RHD+CHD	RHD	CHD	
Definite	2	28	18	1	1	1	61
RHD	2	*35*	1	0	1	1	40
CHD	0	2	*17*	0	0	0	19
RHD+CHD	0	1	0	*1*	0	0	2
Suspected	3	0	0	0	2	3	13
RHD	3	1	0	0	*2*	0	6
CHD	2	2	0	0	0	*3*	7
Total	7	41	18	1	3	4	74

most of the previous diagnoses of rheumatic heart disease fell into the extra group.

Three children were thought to have both definite rheumatic and definite congenital heart disease. The three combinations diagnosed in the field were mitral stenosis plus atrial septal defect, mitral insufficiency and stenosis plus ventricular septal defect, and mitral insufficiency and stenosis plus subaortic stenosis. Two of these children were in the follow-up group. One was diagnosed on more detailed study as having combined heart disease and the other as having rheumatic heart disease only.

Evaluation of the Screening Procedure

Any time a case-finding program is contemplated, an effort must be made to estimate the efficiency of the test being used as the tool for finding cases. Such an estimate requires a standard of reference. For the present study, diagnosis made by simple stethoscopic screening will be taken as the measure of the tool and the diagnosis following detailed study in the clinic will be taken as the standard of reference. Such a comparison is necessarily limited to those who were known to be followed up with detailed diagnostic studies, a total of 74 children in this case. The details are shown in Table 7.

It appears that in this small sample of the total persons with a field diagnosis of suspected or definite heart disease there was agreement with clinic diagnosis in 62, or 84%, of 74.

From Table 7 it can also be seen that for those cases thought to be definite heart disease on both screening and follow-up clinic diagnosis there was agreement as to etiologic type in 53, or 93%, of the 57 cases.

In an attempt to determine the specificity of diagnosis of lesions of congenital heart disease by simple screening examination, an estimate was made of the frequency of agreement between the field diagnosis and that resulting from detailed study made later. There were known to be 16 children who were diagnosed in the field as having definite congenital heart disease and who were later given a complete diagnostic study in one of the cardiac clinics of the University of Colorado Medical Center, with which the field examiners were associated. For these 16, there was 100% agreement as to the fact of heart disease, 93% agreement as to etiologic type (one field diagnosis of congenital heart disease was changed to rheumatic heart disease after study in the clinic), and 75% agreement as to the specific lesion.

It is admitted that no hard and fast conclusions can be based on such a small group. However, it does indicate that where screening examinations are done by competent pediatric cardiologists a fair degree

TABLE 8.—*Comparison of Screening and Follow-Up Diagnoses*

Screening Diagnosis	Standard of Reference *			Total
	No Heart Disease	Definite Heart Disease	Suspected Heart Disease	
Definite heart disease	2	57	2	61
Suspected heart disease	5	3	5	13
Total	7	60	7	74

* Findings by detailed clinical study.

of accuracy can be achieved in diagnosis of specific lesions of congenital heart disease.

The foregoing estimates refer to the specificity of the screening test, or the relationship of true positives (field diagnosis confirmed on follow-up in cardiac clinics) to the total positives by field diagnosis. Equally important is the estimate of sensitivity of the test. This cannot be made, however, since there are no data as to the number of false and true negatives resulting from the screening test.

There was one known false negative and probably more. Because of a field diagnosis of "probable physiologic murmur," the suspicion raised lead to further study. A coarctation of the aorta was found and corrected surgically.

Without data as to sensitivity, the efficiency of screening procedure cannot be estimated. An estimate of specificity alone is not enough.

Summary

Report is made of the characteristics of heart disease found in 11,151 sixth-grade school children and 1702 other children in 41 of Colorado's counties. The expectancy of finding heart disease in the two different groups is illustrated. Data are presented to indicate the problems of case-finding in terms of certainty of diagnosis of heart disease.

The distribution of heart disease by etiologic type and by lesion is shown. Evidence is presented as to the diagnostic accuracy of a simple cardiac examination carried out under field conditions by teams of physicians expert in pediatric cardiology.

Where field diagnoses of definite or suspected heart disease were followed up by detailed diagnostic studies within a period of two years there was agreement as to certainty of the presence of heart disease in 84% of cases.

The efficiency of the simple stethoscopic screening procedure for detection of heart disease in mass screening of children cannot be estimated from the data available. This is true because there is no standard of reference which could be applied to all those screened. There is no way of knowing how many false-negative tests occurred.

This paper is presented for the benefit of those who may consider undertaking a similar case-finding program.

University of Michigan, School of Public Health, Ann Arbor, Mich. (Dr. Dodge).

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Congenital Aortic Stenosis in Young Children

With Special Reference to Phonocardiography and Indirect Tracings of the Arterial Pulse

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Introduction

The diagnosis of congenital aortic stenosis in children can be missed easily. Many of the symptoms indicating aortic stenosis in an adult, like dyspnea on exertion, dizziness with occasional syncope, or left ventricular hypertrophy, were not present in most of our patients. In childhood incipient or moderate forms of aortic valvular disease prevail.

Several authors [1-4] have stressed the importance of tracings of the arterial pulse wave, taken from the brachial or carotid artery. We feel that direct tracings obtained by puncture of a main artery cannot be performed routinely because of the discomfort to the child. Moreover, the tracings from the brachial or radial artery are likely to be less typical than those from the carotid artery, which is closer to the aortic valves. Also, curves derived from the arterial wall may give more information in valvular aortic stenosis than tracings of the intraluminar pressure (Fig. 1). For these reasons, we have obtained indirect tracings from the carotid artery, which can be done easily even in young children. This paper presents the additional evidence supplied by arterial-pulse-wave tracings that supported the diagnosis of congenital aortic stenosis in 38 children. In 10 additional patients the diagnosis was established prior to the introduction of arterial pulse tracings.

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From the Pediatric Department of the University of Amsterdam; Head, Prof. Dr. S. van Creveld.

Methods

Tracings were made by placing a pulse-capsule with appropriate plastic membrane over the carotid artery. The pulse waves were transmitted by a short piece of rigid polyethylene tubing to a piezoelectric microphone which was connected to a multichannel direct-writing electrocardiograph (type Mingograph No. 42). A similar technique has been used by Smith.[5] The normal carotid artery pulse wave shows a sharp rise after the first heart sound, followed by a gradual decline towards the dicrotic notch. A small second peak caused by the rebound of the blood stream against the closed aortic valves may follow. In aortic stenosis the rise after the first heart sound is prolonged and may be interrupted by an anacrotic notching. Anacrotic notches, however, can be found also in patients not suffering from aortic stenosis. Vibrations are seen near the summit or start shortly after the beginning of the ascending leg of the curve, while on the top a plateau may be formed (Fig. 2).

Investigations

Among 900 patients seen in the heart station of the pediatric clinic of the University of Amsterdam, 48 were recognized to have congenital aortic stenosis on the basis of typical changes in the phonocardiogram and carotid artery curve. The presence of the murmur from birth on, or at least from early infancy, and the absence of a history of rheumatic fever indicate the congenital origin of this condition. Of the 48 patients 34 were boys and 14 were girls. The age when the heart murmur was first detected was under 2 years in 26 cases, 2 to 4 years in 8 cases, 4 to 6 years in 4 cases, and 6 years or over in 10 cases.

Clinical Manifestations.—Left ventricular hypertrophy was present in only half of the patients. The maximal intensity of the

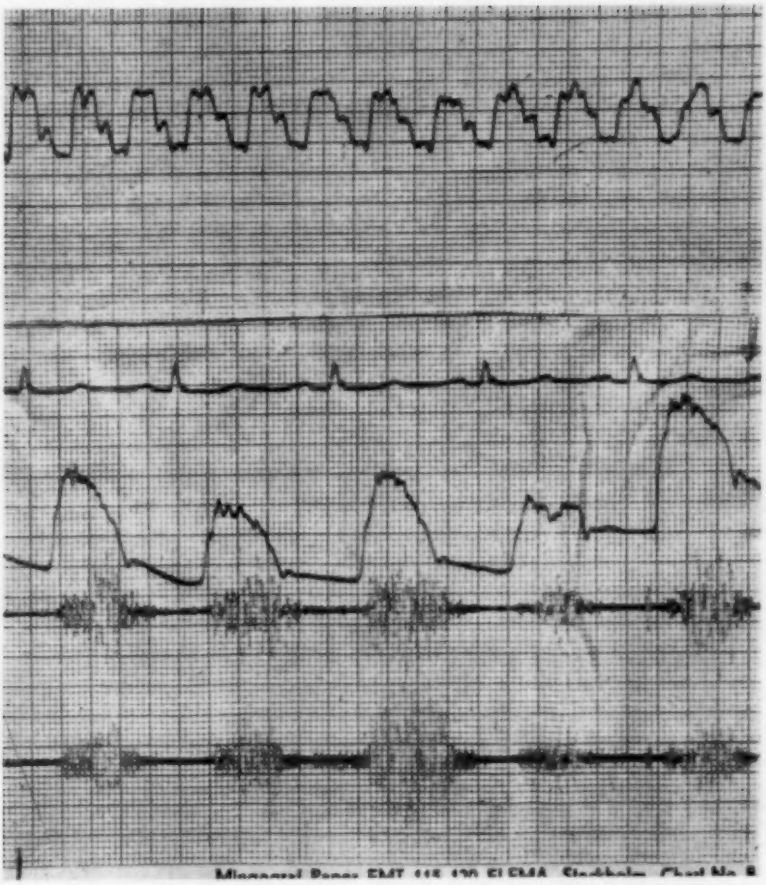

Fig. 1.—Upper curve, tracing obtained during catheterization of the aorta via a patent duct; lower curve, indirect tracing of the carotid artery pulse in the same patient.

systolic murmur was oftenest located in the second right intercostal space, but it was not seldom on the left of the sternum (Table 1). A systolic murmur Grade 1 to 3, loudest over the third or fourth intercostal space on the left side of the sternum, or even radiating towards the apex, was in 17 cases the only auscultatory sign of valvular aortic stenosis.

Phonocardiography showed a diamond-shaped systolic murmur, starting immediately after the first sound.

If the stenosis is severe the murmur may occupy the whole length of the systole, but an interval is always present between the end of the murmur and the second sound. However, in cases of severe stenosis this interval may be very small.

In contrast to the findings in rheumatic aortic valvular disease, diastolic murmurs were rare and occurred more frequently when the child was older. In two children diastolic murmurs were absent at the first examination but appeared at a later age. Both patients may be assumed to have bicuspid aortic valves that were slightly stenosed at birth but became incompetent at a later time.[6]

Arterial Pulse Tracings.—Anacrotic notching and vibrations were present in all patients. A reproduction of a typical tracing of the carotid artery pulse in congenital

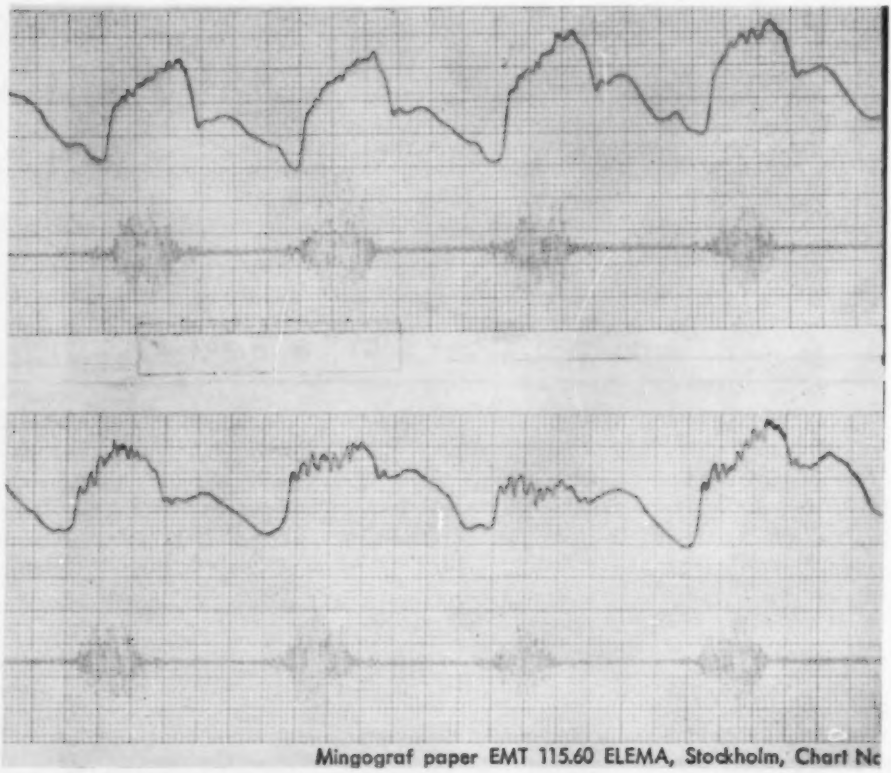

Fig. 2.—Tracings of carotid artery pulse typical for aortic stenosis. Phonocardiogram demonstrates early diamond-shaped systolic murmur.

aortic stenosis is given in Figure 2. Measurements of various constituents of the curve were done in 19 cases showing evidence of left ventricular hypertrophy and in 19 other cases of congenital aortic stenosis without hypertrophy. Tracings obtained in 34 control children were similarly analyzed. The mean values for ascending time, peak time, their combination, and the ascending-time index are given in Table 2. The Wilcoxon test was used to determine whether differences in mean values had statistical significance.

TABLE 1.—*Location of Maximal Intensity of Murmur*

	Cases, No.
2d right intercostal space	25
2d-3d left intercostal space	17
Both left and right *	6

* There were one case of patent duct and one of pulmonary stenosis, respectively, and two coarctations.

The ascending time is the time elapsing between the onset and the peak of the ascending leg of the curve. The mean value for the aortic stenosis group (0.13 second) is greater than in the control group (0.096 second). The peak time, e. g., the interval between the peak of the curve and the onset of the dicrotic notch, is not different in the two groups. The precise determination of the end of the ascending leg of the curve is occasionally difficult, owing to the vibrations occurring at the top of the curve in aortic stenosis. This partly explains why the scatter of individual values in the patients is so much larger than in the controls. For this reason, the mean value was calculated for the combined ascending and peak times. This resulted in slightly less variation of individual values but also in relatively less difference between the mean

TABLE 2.—*Comparison of Various Mean Values Obtained by Analysis of Carotid Artery Pulse Wave Tracings in Normal Children and in Children with Congenital Aortic Stenosis*

	Determinations, No.	Ascending Time *	Peak Time *	Asc. Time & Peak Time *	Asc. Time Index, % *
(*a*) Normals	34	9.6±0.31	15±0.43	25±0.38	16±0.76
Aortic stenosis					
(*b*) Without ventricular hypertrophy	19	13±0.96	14±1.2	28±0.84	19±1.7
(*c*) With ventricular hypertrophy	19	13±0.78	16±1.3	29±1.3	22±1.7
(*d*) Combined	38	13±0.78	15±0.85	28±0.83	21±1.4
Probability					
a vs. *b*		<0.001		<0.001	<0.001
a vs. *c*		<0.02		<0.005	<0.001
a vs. *d*		<0.001		<0.001	<0.001
b vs. *c*					<0.01

* Seconds/100±S. E. M.

values for patients and controls. Finally, the ascending-time index was calculated by expressing the ascending time as a percentage of the total pulse period.[7] An increase in the mean value for this index is present in patients with left ventricular hypertrophy, as has been stressed by Gerritsen.[8]

Comment

From our data it can be concluded that the ascending time and the ascending-time index are prolonged in aortic stenosis. Although the probability that differences in mean values for control children and children with congenital aortic stenosis are due to chance is very slight, the individual values show a considerable variation, especially in aortic stenosis (Fig. 3). Therefore, the measurement of ascending time or ascending-time index in individual cases will contribute evidence to the diagnosis of aortic stenosis in only a minority of the patients.

It has to be realized that the ascending time does not depend on the degree of aortic stenosis only but also on the presence of compensatory hypertrophy of the left ventricle and of the elasticity of the aorta. Individual values for ascending time and ascending-time index will reflect the influence of various forces, only one of them being the degree of aortic stenosis. No correlation was found between the prolongation of the ascending time and the severity of the stenosis as derived from the presence of left ventricular hypertrophy (Fig. 3).

In 14 patients an additional congenital malformation of the heart was present (Table 3). The combination of coarctation of the aorta and malformation of the aortic valves has been reported before.[9] Patients with a patent duct or coarctation combined with valvular aortic stenosis have been operated upon. In those cases the continuous murmurs of patent duct and the late systolic murmurs of coarctation disappeared, while the characteristic early systolic murmur and the abnormal carotid artery curve remained. When surgical correction is contemplated in these patients a complete diagnosis should be made beforehand to prevent disappointment of parents and surgeon. In none of our cases was the valvular stenosis severe enough to preclude surgical treatment of a patent duct or coarctation of the aorta; on the contrary, all those patients have markedly benefited from it. The diagnosis of concomitant ventricular septal defect was made on evidence obtained by cardiac catheterization. In one case the simultaneous presence of valvular pulmonary and aortic stenosis has been established (Fig. 4).

Since we use indirect arterial pulse tracings routinely in children with heart disease, the number of cases of valvular aortic stenosis is relatively large. Many of these children had erroneous diagnoses before (Table 4), or only their concomitant heart malformation had been recognized.

We are well aware that anatomical or surgical proof of the presence of aortic stenosis is still lacking in our cases. Though

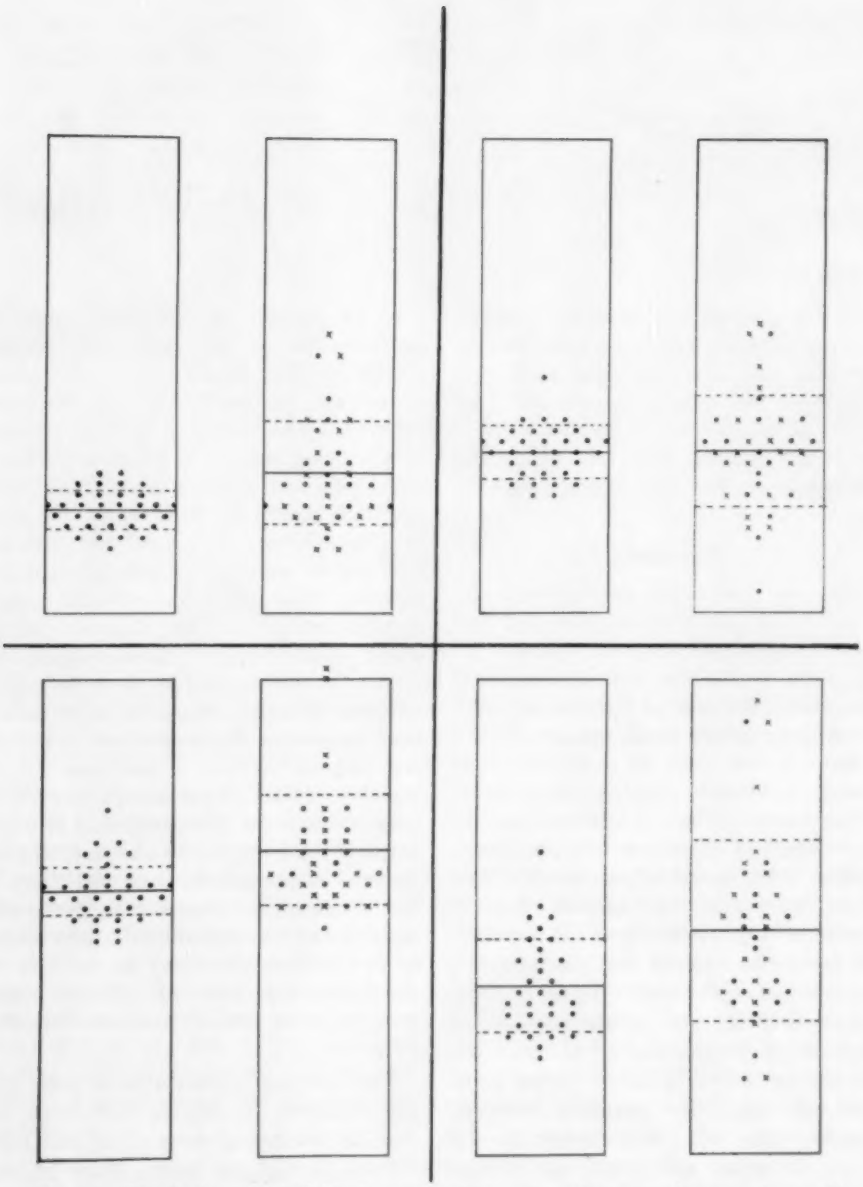

Fig. 3.—Distribution of individual measurements of various constituents of carotid artery curve, with mean (—) and standard deviation (---) for ascending time (upper left), peak time (upper right), ascending time and peak time combined (lower left), and ascending-time index (lower right). Values obtained in control children are shown on the left columns; those from patients with aortic stenosis, in the right columns. Patients with left ventricular hypertrophy are indicated by an X.

TABLE 3.—*Malformations of the Heart Concomitant with Congenital Valvular Aortic Stenosis*

	Malformations, No.
Vascular ring	1
Patent duct	1
Coarctation	5
Valvular pulmonic stenosis	1
Ventricular septal defect	4
Right and left pulse difference	1
Atrial septal defect	1

in most of the affected children a carotid shudder can be detected, its palpation may be difficult. The carotid artery curve and phonocardiography are each indispensable in the cardiologic examination of children. When these tracings are conclusive, the diagnosis of valvular aortic stenosis can be made with confidence, even when signs of left ventricular hypertrophy are absent by ECG or x-ray examination. However, when hypertrophy of the left ventricle is

TABLE 4.—*Diagnosis in Thirty-One Cases Before Introduction of Carotid Artery Curves*

	Cases, No.
Mitral insufficiency	1
Ventricular septal defect	6 *
Atrial septal defect	1
Coarctation	3 †
Pulmonary stenosis	3 ‡
Vascular ring	1
Aortic stenosis	17

* Two cases with ventricular septal defect and aortic stenosis
† All had coarctation besides aortic stenosis.
‡ One case with pulmonary and aortic stenosis.

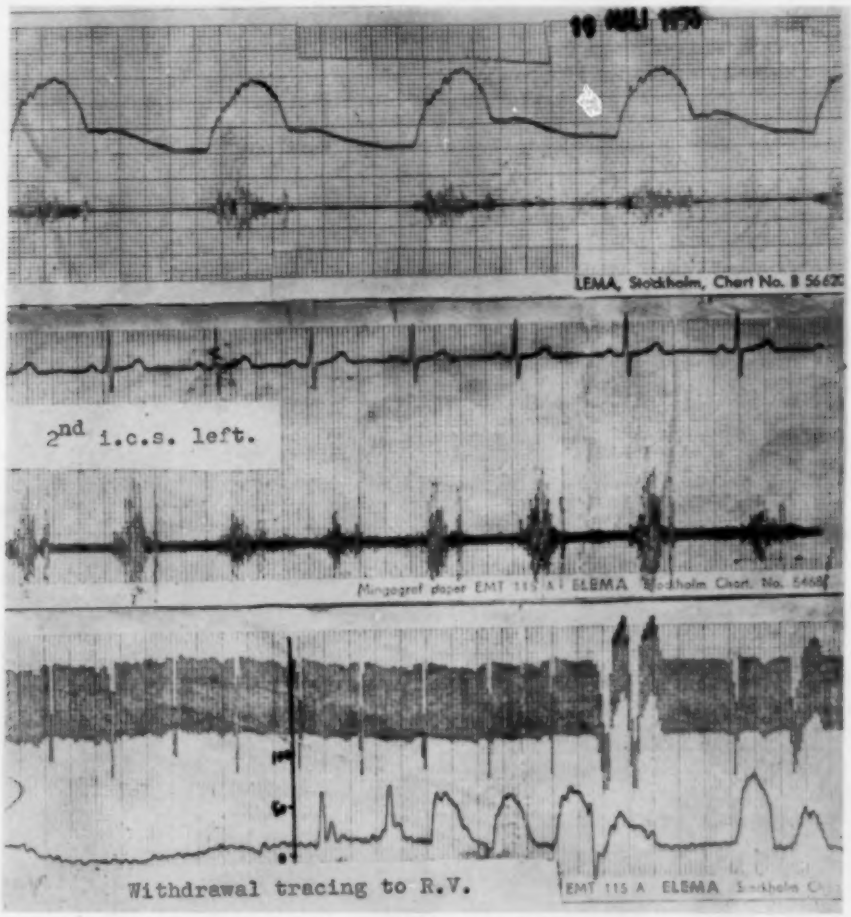

Fig. 4.—Above, typical curve for aortic stenosis. Middle part, diamond-shaped early systolic murmur. Lower part, withdrawal tracing from pulmonary artery to right ventricle, demonstrating the presence of valvular pulmonic stenosis.

present a slight poststenotic dilatation of the ascending aorta may be seen at fluoroscopy. Calcification of the aortic valves could never be demonstrated in our cases, though it may be found in adults with congenital valvular stenosis. In our children the aortic stenosis was probably of congenital origin, because of the early age when the murmur was discerned for the first time, i. e., when rheumatic fever is still very rare. Moreover, no history of rheumatic fever could be elicited in our cases.

Combination with other malformations of the heart is frequent and lends further support to the hypothesis that valvular aortic stenosis in these children is of a congenital nature. In one of our patients subacute bacterial endocarditis has developed. It is well known that a malformed aortic valve is more susceptible to bacterial infection.

No clear difference is known in auscultatory and x-ray findings and in pulse-wave tracings from patients with valvular aortic or subaortic stenosis. Catheterization of the left heart may give more information but has not been performed in our patients. It is thus possible that in some cases of our series the site of the stenosis may be subaortic rather than valvular. Catheterization of the right heart has been done only to confirm the presence of other congenital defects. Subjective signs were notably absent in the majority of our cases. Complaints about shortness of breath could not be found in most children, and only two may have had an occasional syncope.

Prognosis.—Progress of the disease during childhood usually gives minor complaints only, but some cases may show progressive enlargement of the heart. Then cardiac failure and syncopes may follow in short time. Therefore, regular examination is necessary. Sudden death has occurred in three of our patients, in all after relatively heavy physical exertion: One died during a bicycle race; one, during a forced walk, and one, during a painful reposition of a broken arm. The importance of a timely diagnosis is evident, so that physical activities can be curtailed. Even minor surgical procedures, when painful, should be performed with precaution.

Therapy.—Surgical correction of valvular aortic stenosis has often been performed in recent years. Though the mortality in children is lower than in adults, the risk of aortic insufficiency is not to be minimized. The occurrence of aortic insufficiency as a result of the procedure increases the necessary cardiac output by two to four times.[10]

In some of our patients progressive enlargement of the heart and syncopes have made surgical treatment mandatory.

Summary and Conclusion

In young children the presence of congenital aortic valvular stenosis may not be detected, especially as the stenosis is only mild and sometimes combined with other, more serious, malformations of the heart. We have found indirect tracings of the carotid artery pulse and phonocardiography to be most useful adjuncts in the examination of the heart, ones that can be easily performed even in very young children. The findings in 48 children suffering from congenital aortic stenosis are presented.

Various constituents of the carotid artery pulse tracings were measured and compared with the values of normal children. Although the ascending time and ascending-time index are each prolonged in aortic stenosis, it is also shown that determination of these values in individual cases will be helpful in establishing the diagnosis in only a third of the patients.

The diagnosis is important because under strain these children are liable to sudden death. Especially when the risk of surgical correction will have diminished, more patients may become eligible for surgery.

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Prednisone in the Treatment of Allergic Diseases in Children

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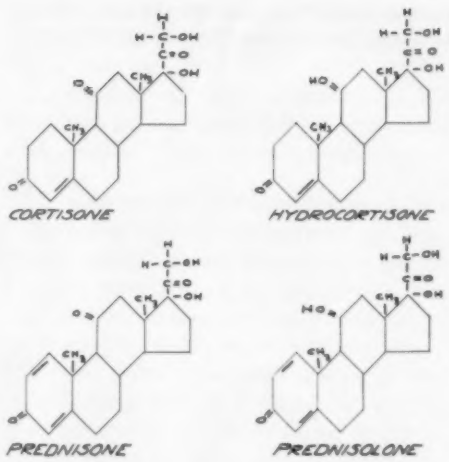
Two recently synthesized and developed steroid hormones, prednisone and prednisolone, have given promise of having all the advantages of their precursors, cortisone and hydrocortisone, while obviating many of the undesirable side-effects of the older preparations.[1,2] These side-effects, which were noticeable even with the short-term use of the older preparations, included sodium and water retention, potassium depletion, moon facies, and hypertension.

Prednisone is an analogue of cortisone, whereas prednisolone is a similar analogue of hydrocortisone. They are obtained by the dehydrogenation of the carbon atoms in Positions 1 and 2 of the steroid nucleus, resulting in a double bond between C_1 and C_2 (Fig.).

Clinically, they appear to have from three to five times the effect of cortisone and from two to four times the effect of hydrocortisone.[3,4] There appears to be little difference between the clinical effectiveness or dosage of prednisone and of prednisolone.[3-5] Therefore, we decided, as a matter of simplification, to use prednisone exclusively when streoid therapy was indicated for allergic conditions in this series of patients.



Several reports on the use of these newer steroids in the treatment of allergic conditions have recently appeared. Most of these have concerned themselves with adult patients. Most of the patients treated were on long-term therapy. For instance, Criep [3] reports on 18 children out of 96 patients treated. Arbesman and Ehrenreich [4] reported on 11 children out of 101 patients. Brown and Seideman [6] reported on the use of these hormones in 157 patients with hay fever or allergic rhinitis but did not specify how many children were treated. More recently, Siegel and associates [8] reported on the use of prednisone in the treatment of allergic disorders in 16 children.

The purpose of this report is to detail our experience using prednisone in 85 children with acute allergic manifestations and to emphasize not only its effectiveness but its great value and safety when used primarily for short-term therapy.

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The Schering Corporation supplied the prednisone (Meticorten) used in this study.

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Method and Materials

The patients discussed in this report are either from private practice or from the allergy clinic of the Children's Hospital of Michigan. All patients underwent complete diagnostic studies, which included a complete history, physical examination, and laboratory studies (complete blood cell count, urinalysis, chest x-ray, and tuberculin test; also, a sweat test when indicated). All patients received skin tests by both scratch and intradermal methods, when indicated.

Following the initial study, a program which included environmental precautions, avoidance of specific foods and inhalants, desensitization (immunization), and the careful and specific use, when indicated, of medications, such as antibiotics, chemotherapeutic agents, bronchodilators, antispasmodics, and expectorants, was instituted for each patient, depending upon the diagnosis made in each case.

Only when it appeared that these measures would not keep the patient free of alarming symptoms or when the patient presented symptoms severe enough to delay the initial investigative study was prednisone resorted to.

The use of prednisone was therefore restricted to tiding a patient over the period during which a diagnostic study was carried out, for alleviating acute episodes of various allergic states, and for enabling long-term desensitization therapy to continue uninterrupted. It is generally agreed that it is not a substitute for adequate allergic diagnosis and treatment.

During the time these patients were receiving prednisone, they were under close medical supervision. Their weight, blood pressure, and urine were checked. Their temperatures were noted and nose, throat, and chest were examined at each visit. All patients were given only enough prednisone for one week's treatment in the dosage schedule to be discussed below. A certain number of patients required more than one course of prednisone. Only 1 of the entire 85 patients requires continuous maintenance therapy.

Other treatment, including specific desensitization, antibiotic therapy, and symptomatic measures, was continued during the time prednisone was administered.

Thirty-two of the eighty-five patients in this series had previously been treated with either cortisone, hydrocortisone, or corticotropin (ACTH). While no direct comparison of the efficacy of prednisone to that of the older steroids or to corticotropin will be made in this paper, it is our clinical impression that, if treatment with prednisone is begun with the correct dosage, clinical improvement in the status of these patients is as good, or better, than with the older steroids or corticotropin, with few or none of the side-effects engendered by the use of the older preparations.

TABLE 1.—*Prednisone in Acute Allergic States in Children*

Diagnosis	Patients, No.
Bronchial asthma	55
Atopic dermatitis	11
Perennial allergic rhinitis	5
Seasonal pollinosis	13
Urticaria	1
Total	85

Table 1 gives the distribution of our patients according to the allergic diagnosis made in each case and shows the disease for which prednisone was used. While 85 patients are discussed here, because of the occurrence of two or more allergic states in more than one child, we actually were treating 98 separate but closely related disease entities. The 85 children ranged from 2 to 17 years of age. There were 55 boys and 30 girls.

Table 2 indicates the dosage used. It has been our practice to begin treatment in patients over 5 years of age with 10 to 20 mg. of prednisone per day in divided doses and subsequently to decrease the dose according to the manner outlined in the Table. In younger children, less prednisone was used initially and the dose was reduced in a fashion similar to that outlined in Table 2. However, there is no direct relationship between age and dosage of prednisone. The younger children required only slightly less total dosage than the older ones.

Results

I. Bronchial Asthma.—Fifty-five children with bronchial asthma were given prednisone. Of the 55 patients, 18 have thus far required two courses of the drug, 5 have required three courses of the drug, and 1 patient is on continuous maintenance therapy.

In reviewing the clinical course of these 55 patients, it is interesting to note that prednisone was necessary shortly after the initial visit in 30 of these patients. It was

TABLE 2.—*Dosage of Prednisone in Children*

Day	Dose, Mg.	Times Daily
1st	5	2–4
2d	5	2–3
3d	5	2–3
4th	5	1–2
5th	5	1
6th	2.5	1
7th	2.5	1

required prior to the inception of standard allergic management and procedures, in order to bring the acute symptoms under control so that allergic investigation could be initiated. Of these 30 patients, all of whom have now been treated for more than six months, only 5 have subsequently required more prednisone.

Respiratory infection was the initiating mechanism in necessitating the use of prednisone in 60 out of the 82 courses of prednisone given to these 55 asthmatic patients. Prednisone was given in the manner outlined in Table 2 along with full doses of the appropriate antibiotic or chemotherapeutic agent and other symptomatic therapy. Twelve of the remaining twenty-two courses were given to patients suffering from asthma associated with seasonal pollinosis. There was no definite etiologic agent precipitating asthma for the remaining 10 courses of prednisone. When there was no definite evidence of infection, antibiotics were not given along with the prednisone. We feel that one should not wait until status asthmaticus develops before using predisone. If the patient does not experience relief within 12 to 24 hours after the onset of severe wheezing by the use of bronchodilators, expectorants, and antibiotics, if necessary, then predisone is begun as outlined in Table 2.

When prednisone is given in this manner, relief of wheezing and dyspnea is dramatic and occurs within 8 to 12 hours after prednisone therapy is begun. Antibacterial and symptomatic therapy is continued along with the prednisone, and the former is continued for 48 hours after cessation of prednisone.

When prednisone was administered in this way, we had only 6 patients of the 55 whose asthma recurred immediately after the predisone was stopped. Of these six patients, four could be maintained on symptomatic therapy and two required another course of prednisone. One of these two is the patient requiring continuous maintenance therapy. This patient is extremely sensitive to even minute amounts of antigenic material, and desensitization has been difficult and slow to accomplish. However, when taking 5 to 7.5 mg. of prednisone per day he is symptom-free and able to lead a normal existence. He has been taking this modest dose for five months and has shown no evidence of moon-face, hypertension, undue weight gain, or potassium depletion.*

We have been impressed with the efficacy of prednisone used in the manner outlined. Status asthmaticus was not seen in this group. None of these 55 patients has required hospitalization for status asthmaticus since he has been treated as outlined above.

II. Atopic Dermatitis.—Eleven patients suffering from severe generalized atopic dermatitis required the systemic use of predisone. Of these 11 patients, prednisone was required in 8 at the onset of treatment to obtain sufficient normal skin in order to do selected scratch and intradermal tests. It was necessary in the other three patients because of a severe flare-up during desensitization treatment.

Following the administration of prednisone to these children, remission of the dermatitis was noted in 36 to 48 hours after the initial dose was given in all cases. This was manifested by decrease in erythema, diminished oozing, and a marked subjective relief of pruritis. Prednisone was administered as outlined in Table 2. However, it was noted that a decrease in dosage below a certain level—usually below 10 mg. per day—caused a recurrence of the dermatitis, which then required larger doses to be suppressed.

As with the use of the older steroids and corticotropin, it was noted that the dermatitis recurred promptly after the cessation of systemic prednisone therapy unless, by the time of completion of such therapy, other measures, which included specific desensitization, elimination of environmental and

* This patient's dosage has gradually been reduced to 2.5 mg. twice daily and at time of publication, he still has not shown any undesirable side-effects.

contact factors, and dietary and local treatment to combat the dermatitis, had been effective.

We have not found it necessary to use systemic prednisone in milder cases of generalized atopic dermatitis nor in cases of localized flexural eczema, relying in these instances on the judicious use of local measures, which have included antiphlogistic soaks, topical steroids, coal tar preparations, and antibiotics when necessary, in addition to specific desensitization.

In the main, therefore, with atopic dermatitis, systemic prednisone was used initially when necessary so that the usual methods and tools of allergic management could come into play for the long-term therapy of this disease.

III. Perennial Allergic Rhinitis and Seasonal Pollinosis.—Eighteen patients who suffered from either seasonal pollinosis or perennial allergic rhinitis are included in this study. Five patients had perennial allergic rhinitis; thirteen suffered from seasonal pollinosis. They are included together because of a similarity of clinical symptomatology and clinical responsiveness to both symptomatic and prednisone therapy. Patients who suffered from seasonal pollinosis or perennial allergic rhinitis which was complicated by bronchial asthma were included in the group of cases of bronchial asthma.

Ten of the thirteen patients suffering from seasonal pollinosis presented themselves for the first time during their pollen season. They were suffering acutely from lacrimation, conjunctivitis, rhinorrhea, sneezing, and nasal obstruction and were not relieved by the use of antihistamines, eye drops, nose drops, or other symptomatic treatment. The remaining three patients were undergoing specific treatment for pollinosis and suffered relapses during their season.

Prednisone was used to relieve acute symptoms of nasal obstruction temporarily in all five of the patients suffering from perennial allergic rhinitis while they were undergoing specific desensitization.

Relief of symptoms in all 13 children resulted from the use of prednisone in 24 to 48 hours. It was necessary to give the 10 patients suffering from seasonal hay fever, who had not previously received desensitization, maintenance doses of from 5 to 10 mg. of prednisone per day for 5 to 7 days and a few as long as 14 days while treating them co-seasonally, with small amounts of intradermal antigens. This somewhat longer period of treatment did not result in any apparent side-effects.

The use of prednisone in five children with perennial allergic rhinitis was likewise excellent, giving them relief from severe symptoms of nasal obstruction and sneezing while allowing desensitization to go on uninterrupted. Discontinuance of prednisone in these cases did not result in recurrence of symptoms while the patients were under specific allergic management.

IV. Urticaria.—Only one child with chronic urticaria was treated with prednisone. This child exhibited a chronic generalized urticaria which was intensely pruritic. Intensive diagnostic studies which included careful and complete history for food or drug relationships which might have caused the urticaria failed to reveal the etiologic agent; physical examination and laboratory studies failed to show hidden infection or any other definitive cause. Scratch and intradermal skin tests showed some positive reactions, and prednisone was begun at the onset of desensitization with specific inhalants. The patient's urticaria cleared completely while she was taking prednisone, but it relapsed after prednisone was withdrawn. She has subsequently had one other course of prednisone, during which her condition again cleared, and relapsed occurred after withdrawal of prednisone.

Our experience in this case is similar to other reports concerning the use of steroids in this disease; that is, unless the offending cause is discovered and removed, the

urticaria returns promptly when the steroid is stopped.[7]

The intensity of the patient's urticaria has gradually lessened over a period of three months, and it was felt that her symptomatology did not warrant the risks of long-term prednisone therapy.

Comment

It is evident from the data presented that we have found prednisone an extremely useful drug for short-term use in the treatment of various acute allergic states. We have found, as have others, that it is from two to four times as effective in its antiallergic properties as hydrocortisone. While somewhat dependent on age, weight, and severity of the allergic process, the dose required to suppress acute symptoms initially and for maintenance was found to be relatively high in comparison with that reported for adults. This observation is in agreement with findings on the use of other steroids in children.[8]

Recent work by various investigators relating changes in plasma protein composition to steroid administration reveals some of the metabolic effects of these hormones on various body constituents.

Serum paper electrophoresis performed on 121 asthmatic children by Tuft[9] showed lowered albumin and elevated α_2- and γ-globulin. The effect of steroids on the electrophoretic pattern was to increase albumin and α_1-globulin, to exert no effect on previously elevated α_2-globulin, and to decrease γ-globulin levels toward normal.

Siegel et al.[10] reported the results of 152 determinations of plasma 17-hydroxycorticosteroids in 57 asthmatic and 32 normal children. Included in this group of steroids are cortisone and hydrocortisone, the latter being the principal adrenocortical hormone. Plasma 17-hydroxycorticosteroid levels were determined in 57 asthmatic children at four stages in this disease: asymptomatic, mild, moderate, and severe.

The plasma levels of 17-hydroxycorticosteroids were significantly higher in patients with moderate or severe symptoms, as compared with those in the asymptomatic or mild groups. In patients in the latter two groups, the 17-hydroxycorticosteroid levels were not statistically different from those of the normal controls.

Siegel and co-workers also recorded the results of 57 determinations of plasma 17-hydroxycorticosteroid levels in 21 allergic children receiving variable amounts of prednisone and prednisolone. They found that the levels in these children correlated directly with the amount of prednisone or prednisolone given, but no critical hormone level at which the majority of patients became asymptomatic could be determined.

The effects of prednisone in various pulmonary-function studies were noted by Barach et al.[11] in a group of adult patients. In 21 of 30 patients tested both before and after a course of prednisone they found marked improvement in vital capacity and in the fast-expiratory-volume test. In eight patients tested before and after prednisone they found marked improvement in the maximal breathing capacity. These studies indicate a definite relief of the bronchospastic state of these patients and indicate that prednisone apparently exerts its beneficial effect in bronchial asthma by reducing bronchial spasm.

In the lessened number and severity of side-reactions prednisone has a distinct advantage over its predecessors. Especially in the short-term use of prednisone, low-sodium diets and the supplemental use of potassium are not necessary. We have not encountered excessive weight gain, hypertension, or any other major or minor side-effect commonly associated with the use of steroids when we have used them in the manner outlined above.

However, this it not to say that prednisone is not a potent agent. Recently, a series of articles by Good et al.[12] clearly demonstrates the inherent danger in prolonged steroid administration in a variety of disease states.

They report anasarca with pulmonary edema, hypertension with encephalopathy,

hypopotassemic shock, thrombosis of the central retinal artery resulting in blindness, status epilepticus due to fluid retention, paranoid schizophrenia, septicemia, peritonitis, septic arthritis, and osteoporosis with pathologic fractures as serious untoward reactions to large doses of the steroid hormones, including prednisone and corticotropin, given over extended periods of time and occurring in pediatric patients.

Experimentally, they have found steroids enhancing the carcinogenic effect of certain chemicals and influencing the incidence and rate of development of diffuse degenerative vascular diseases as well as the activation of latent virus infections. Other reports have documented deaths due to varicella in cortisone-treated children. Good and his associates,[14] however, have not observed any "serious untoward reactions" to the steroid hormones when small doses have been used over short periods of time, such as we advocate.

We, therefore, feel strongly, in view of the above evidence, that, although the addition of prednisone to our armamentarium has given us a potent antiinflammatory agent which is extremely useful in combating acute manifestations of various allergic states, it is not a substitute for careful and specific allergic diagnosis and management. We feel that, except for a rare and exceptional case, the long-term use of the drug is rarely indicated and that the drug when so used is fraught with serious risk for the patient.

Summary

Our experiences with the use of prednisone in the treatment of various allergic states in 85 children are presented.

The chemistry of the drug, indications for use, and precautions required when one is using this drug have been discussed.

Prednisone for short-term therapy has been uniformly excellent for alleviating acute episodes of various allergic states, thus facilitating earlier allergic investigation or enabling long-term desensitization therapy to continue uninterrupted. The short-term use of this drug has been almost completely free of the undesirable side-effects noted with the older steroid preparations.

Some of the more recent work regarding the effect of prednisone on plasma protein constituents and on plasma 17-hydroxycorticosteroid concentrations and the effect of prednisone on pulmonary-function studies is reviewed.

We feel that the long-term use of this drug and other steroids in the treatment of allergic diseases in children should be reserved for the very exceptional and extremely rare patients with intractable asthma or other chronic, debilitating allergic state, and evidence to support this viewpoint is presented.

Even in such patients, thorough and persistent efforts to uncover and treat specific and nonspecific causes should be continued, so that eventually steroid therapy can be terminated.

Addendum

Since this paper was submitted, we have treated four children with severe bronchial asthma requiring longer periods of maintenance with prednisone than outlined above. One patient was treated for four weeks, two for six weeks and one for three months with 2.5 to 5 mg. twice daily after initially receiving higher doses. No undesirable side-effects were noticed in these patients.

470 Fisher Bldg. (2).

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Excretion of Thiamine and Riboflavin by Children

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Few reports are available on urinary excretion of thiamine and riboflavin by children, in relation to different food sources in the diet. An opportunity for such study presented itself in connection with a study of utilization of various foodstuffs. Each child in the original study was given in succession a basal diet, which was planned as a diet adequate in all known nutrients, and two experimental diets, wherein one food was substituted at two levels for the given percentage of each food in the basal diet. Thiamine intake varied from 0.47 to 2.83 mg. daily; riboflavin intake, from 0.79 to 3.23 mg. a day. In addition, six children were given diets containing 0.35 mg. or less of thiamine daily until urinary excretion of this vitamin had apparently reached a minimum level or until it was deemed medically desirable to increase the thiamine intake.

Materials and Methods

The data comprise 84 six-day studies and 45 four-day studies of 21 children, 5 girls and 16 boys, who ranged in age from 4¼ to 13 years and in weight from 16 to 42 kg. Choice of age and sex of the subjects was determined largely by availability. One subject was a healthy 12-year-old boy from a poor home who was housed nine months in the study ward and was the subject of seven studies. Two children served as subjects while housed for therapy of squint; these children were indigent patients. The other children came from a large orphanage; their habitual diets approximated those of the lower middle class. Milk and vegetables were available from the orphanage farm; bread was made with enriched flour. None of the children was "saturated" with vitamins before the study. The object of this study was to determine the amounts of thiamine and riboflavin excreted by children ingesting different amounts of those vitamins from foods and to estimate from the results obtained the requirements of children for thiamine and riboflavin.

The children were brought to the study ward in small groups. By allowing the children participation in the planning and by the daily inclusion of a few foods usually considered as special treats, such as ice cream or bananas, whenever the test foods were not well accepted, excellent cooperation was achieved. The success of the study was due as much to the cooperation of the children as to the nursing staff and laboratory.

All diets were planned to be calorically adequate. Occasionally, the children were unable to maintain as high a caloric intake as the National Research Council Allowances provide, and the diet was adjusted to the child's capacity. At times, a child lost a little weight during the 27 days of each group study; sometimes the child gained. In no case were weight changes great enough to be of concern. The caloric intake and distribution of calories for each study are given in Table 1, and two illustrative basal diets are shown in Table 2.

Other than diets, the daily life of the children approximated that of the average school child. They attended the hospital school, had their own playground, and were taken for hour-long walks when weather permitted.

Collection and Analysis.—The child was maintained on each regimen for three days before collections began: Diets and excreta were analyzed for thiamine and riboflavin during two three-day collection periods for each change of diet making up the 27-day series. Usually two or more subjects were given the diet simultaneously. The foods studied included cereals, leg-

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† Dr. Jeans died Oct. 22, 1952.

TABLE 1.—*The Caloric Intake and Distribution of Calories Ingested by the Children of the Study*

Subject	Weight, Kg.	Age, Yr.	Height, Cm.	Diet	Test Food,* %	Total Calories	Calories, %		
							Protein	Fat	Carbohydrate
1	22	6	118.4	Basal		1,596	22	36	42
				Cornmeal †	6.9	1,571	21	35	44
				Cornmeal †	14.2	1,543	20	33	47
2	20	6	115	Basal		1,596	22	36	42
				Cornmeal †	6.9	1,571	21	35	44
				Cornmeal †	14.2	1,543	20	33	47
3	21	6	116.5	Basal		1,596	22	36	42
				Cornmeal †	6.9	1,571	21	35	44
				Cornmeal †	14.2	1,543	20	33	47
4	25	8	125.1	Basal		1,855	19	35	46
				Cornmeal ‡	3.8	1,839	19	34	47
				Cornmeal ‡	6.6	1,832	19	33	48
5	24	6	117.2	Basal		1,855	19	35	46
				Cornmeal ‡	3.8	1,839	19	34	47
				Cornmeal ‡	6.6	1,832	19	33	48
2	21	6	118	Basal		1,718	20	34	46
				Cornmeal §	7.1	1,693	20	32	48
				Cornmeal §	13.6	1,687	19	31	50
6	25	8	131.3	Basal		1,718	20	34	46
				Cornmeal §	7.1	1,693	30	32	48
				Cornmeal §	13.6	1,687	19	31	50
7	41	12	155.6	Basal		2,922	18	37	45
				Cornmeal §	5.5	2,893	17	35	47
				Cornmeal §	12.8	2,815	17	34	49
7	37	12	152	Basal		2,215	19	41	40
				Oatmeal	7.1	2,188	19	40	41
				Oatmeal	13.1	2,177	20	38	42
7	32	12	152	Basal		2,817	16	47	37
				Raw cabbage	2.8	2,642	17	46	37
				Raw cabbage	6.3	2,496	17	45	38
7	38	12	153.4	Basal		2,287	19	35	46
				Peeled oranges	4.4	2,209	19	34	47
				Peeled oranges	9.7	2,085	18	33	49
7	38	12	155.2	Basal		2,653	18	37	45
				Peanuts	26.5	3,688	19	48	33
				Peanuts	33.1	4,081	19	52	29
7	39	12	155	Basal		2,653	18	37	45
				Raw carrot	2.7	2,407	20	43	37
				Raw carrot	6.5	2,367	20	42	38
8	38	13	144	Basal		2,653	18	37	45
				Raw carrot	2.7	2,407	20	43	37
				Raw carrot	6.5	2,367	20	42	38
9	31	10	144	Basal		2,437	18	34	48
				Raw carrot	2.6	2,387	19	35	46
				Raw carrot	5.4	2,222	20	40	40
10	19	7	113.2	Basal		1,583	21	36	43
				Cooked carrot	3.2	1,551	21	35	44
				Cooked carrot	5.8	1,525	21	35	44
11	17	5	103.4	Basal		1,583	21	36	43
				Cooked carrot	3.2	1,551	21	35	44
				Cooked carrot	5.8	1,525	21	35	44
12	24	6	123.6	Basal		1,583	21	36	43
				Cooked carrot	3.2	1,551	21	35	44
				Cooked carrot	5.8	1,525	21	35	44
13	22	6	116	Basal		1,712	20	40	40
				Applesauce	8.1	1,694	19	38	44
				Applesauce	16.4	1,678	18	35	47
14	17	5	96.2	Basal		1,712	20	40	40
				Applesauce	8.1	1,694	19	38	44
				Applesauce	16.4	1,678	18	35	47
15	19	6	105.2	Basal		1,712	20	40	40
				Applesauce	8.1	1,694	19	38	44
				Applesauce	16.4	1,678	18	35	47
7	42	13	156.3	Basal		2,164	17	32	51
				Roast pork ‖	6.9	2,314	20	33	47
				Roast pork ‖	12.4	2,461	23	34	43
4	25	8	126.6	Basal		1,594	17	35	48
				Roast pork ‖	6.9	1,716	21	36	43
				Roast pork ‖	13.9	1,851	27	36	37
5	24	6	118.8	Basal		1,594	17	35	48
				Roast pork ‖	6.9	1,716	21	36	43
				Roast pork ‖	13.9	1,851	27	36	37
16	23.9	9	130.5	Basal		1,757	23	38	39
				Soybean ‖	7.6	1,760	24	38	38
				Soybean ‖	14.9	1,768	25	37	37
17	20.7	8	119	Basal		1,757	23	38	39
				Soybean ‖	7.6	1,760	24	38	38
				Soybean ‖	14.9	1,768	25	37	37
18	22.3	6	114.4	Basal		1,170	23	38	39
				Soybean ‖	7.6	1,173	24	38	38
				Soybean ‖	14.9	1,180	25	37	37
19	16	4	108	Basal		1,170	23	38	39
				Soybean ‖	7.6	1,173	24	38	38
				Soybean ‖	14.9	1,180	25	37	37

* Per cent contributed by test food to total dry weight of diet (dried at 70 C in vacuo).
† Enriched cornmeal.
‡ Common degerminated cornmeal.
§ Whole white cornmeal.
‖ Feeding of the higher level of test food preceded the feeding of the lower level. The order has been changed for the Table to conform to that of the other studies.

TABLE 2.—*Specimen Diets for Two Basal Periods of Study*

Diet for 6-Yr.-Old	Weight, Gm.
Breakfast	
Milk	240
Bread	25
Butter	10
Wheaties	10
Egg	40
Peaches	40
Sugar	5
Midmorning lunch, milk	120
Dinner	
Milk	240
Bread	25
Butter	10
Mashed potatoes	30
Ice cream	40
Ground beef	30
Green beans	30
Banana	40
Midafternoon lunch, orange juice	50
Supper	
Milk	240
Bread	25
Butter	10
Ground beef	30
Spaghetti	30
Tomato juice	60
Apricots	40
Evening lunch	
Graham crackers	10
Milk	120

Diet for 12-Yr.-Old	Weight, Gm.
Breakfast	
Milk	240
Bread	40
Butter	15
Oatmeal	150
Egg	65
Sugar	15
Orange juice	150
Midmorning lunch, milk	120
Dinner	
Milk	240
Bread	40
Green beans	50
Butter	20
Mashed potatoes	75
Ground beef	75
Bananas	65
Ice cream	65
Midafternoon lunch, pineapple juice	150
Supper	
Milk	240
Macaroni	75
Cheese	35
Tomato juice	150
Bread	40
Butter	15
Pears	100
Evening lunch	
Graham crackers	20
Milk	120

unes, fruits, and vegetables, and there was one study of pork.

A complete day's diet was weighed for the laboratory on the last day of each collection period. The foods analyzed, therefore, were from the same sample as eaten by the children. Meats were weighed cooked; the other foods, as purchased.

The customary precautions of acidification of samples, refrigeration, and protection from light were observed. Urinary thiamine was determined by the thiochrome method of Hennessey and Cerecedo[1] as modified by Najjar and Ketron,[2] Egana and Meiklejohn,[3] and Mawson and Thompson.[4] Homogenates of diets and of feces were hydrolyzed with acid and incubated with a phosphatase, and the thiamine was extracted with fresh isobutanol. An internal standard was used in the analysis of each fecal and diet sample. Samples of the substitute foods analyzed in this way usually agreed well with published values. Riboflavin in urine was determined by the fluorometric method of Najjar.[5] For dietary and fecal riboflavin the fluorometric method suggested by Arnold[6] for foods was used.

Validity of Data.—It is usually considered that long periods of constant intake are necessary to stabilize the quantity of any vitamin excreted in the urine. Yet, in normal living, the intake of each vitamin varies daily. Were the 28 series of studies, each containing one nine-day basal period and two nine-day periods with increased amounts of one food, of too short a span to give a valid picture of thiamine and riboflavin excretion for the given intakes?

Among the 84 studies, daily thiamine intake varied from 0.47 to 2.83 mg. daily; however, except for the two peanut studies (Subject 7), the maximum dietary variation from one nine-day period to the next was 0.26 mg. for thiamine and 0.49 mg. for riboflavin. In the majority of studies, the nine-day changes in intake were small and well within the range expected in any child's home dietary. The data thus could be expected to reflect the utilization of these vitamins by children whose normal diets contained approximately the same vitamin intakes as those of the study. Some of the foods studied provided amounts of thiamine very close to the amounts in the basal diets they replaced (carrots, soybean, white cornmeal). The children receiving these foods therefore were receiving a relatively constant intake for 27 days, although the vitamin sources differed somewhat for each 9 days.

Despite the relatively small variation in dietary intake, the validity of using six-day average excretion values after only a three-day preperiod necessitated proof. The findings of the first six months of the study were scrutinized to determine whether, after a change in dietary regimen with its succeeding three-day preliminary adjustment period, thiamine excretions the first three days of collection (fourth to sixth diet days, inclusive) differed materially and consistently from those of the second three-day collection (Days 7, 8, and 9 of diet regimen).

Forty-seven comparisons were available. When the dietary thiamine remained constant within 100μg., the maximum difference between first and second three-day urinary thiamines was 36μg. per day; with dietary thiamine increased by 100μg. to 260μg., the maximum urinary change was 40μg. per day, and when the daily intake was decreased by 100μg. to 190μg. maximum urine thiamine change was only 24μg. Nearly half the compari-

TABLE 3.—*Thiamine and Riboflavin Excretion of Children Given Larger Than Customary Amounts of Single Foodstuffs*

Subject	Weight, Kg.	Age, Yr.	Height, Cm.	Diet	Test Food,* %	Thiamine					Riboflavin				
						Intake, Mg./Day	Excretion U,† Mg./Day	Excretion F,† Mg./Day	I—TX,‡ Mg./Day	UX100,‡ / I %	Intake, Mg./Day	Excretion U, Mg./Day	Excretion F, Mg./Day	I— TX, Mg./Day	UX100, / I %
1	22	6	118.4	Basal		0.79	0.15	0.50	0.14	19	2.42	1.01	0.52	0.89	42
				Cornmeal §	6.9	0.74	0.14	0.24	0.36	19	1.93	0.94	0.42	0.57	49
				Cornmeal §	14.2	0.71	0.15	0.40	0.16	21	1.80	0.92	0.53	0.35	51
2	20	6	115	Basal		0.79	0.11	0.21	0.47	14	2.42	0.81	0.70	0.91	33
				Cornmeal §	6.9	0.74	0.11	0.26	0.37	15	1.93	0.94	0.69	0.30	49
				Cornmeal §	14.2	0.71	0.10	0.23	0.38	14	1.80	0.84	0.76	0.20	47
3	21	6	116.5	Basal		0.79	0.13	0.33	0.33	16	2.42	1.06	0.52	0.84	44
				Cornmeal §	6.9	0.74	0.12	0.19	0.43	16	1.93	0.81	0.58	0.54	43
				Cornmeal §	14.2	0.71‖	0.10	0.24	0.37	14	1.80‖	0.88	0.58	0.34	49
4	25	8	125.1	Basal		1.15	0.22	0.54	0.39	19	2.30	1.11	0.91	0.28	48
				Cornmeal ¶	3.8	1.01‖	0.18	0.33	0.50	18	2.22‖	1.07	0.81	0.34	47
				Cornmeal ¶	6.6	0.93	0.20	0.28	0.45	22	1.91	0.89	0.74	0.28	47
5	24	6	117.2	Basal		1.15	0.19	0.45	0.51	17	2.30	1.17	1.12	0.01	51
				Cornmeal ¶	3.8	1.06	0.16	0.45	0.45	15	2.28	1.03	1.28	—0.03	45
				Cornmeal ¶	6.6	0.93	0.19	0.46	0.28	20	1.91	1.14	1.30	—0.53	60
2	21	6	118	Basal		0.76	0.13	0.36	0.27	17	2.11	0.91	0.80	0.40	43
				Cornmeal #	7.1	0.79	0.15	0.25	0.39	19	1.97	0.92	0.68	0.37	47
				Cornmeal #	13.6	0.82	0.15	0.11	0.56	18	1.65	0.94	0.80	—0.09	57
6	25	8	131.3	Basal		0.76	0.12	0.54	0.10	16	2.11	1.10	1.24	—0.23	52
				Cornmeal #	7.1	0.79	0.15	0.42	0.22	19	1.97	0.99	1.31	—0.33	50
				Cornmeal #	13.6	0.82	0.12	0.37	0.33	15	1.65	0.89	1.10	—0.34	54
7	41	12	155.6	Basal		1.57	0.22	0.50	0.85	14	2.75	1.39	1.08	0.28	51
				Cornmeal #	5.5	1.45	0.25	0.50	0.70	17	2.70	1.31	1.16	0.23	49
				Cornmeal #	12.8	1.26‖	0.24	0.47	0.55	19	2.45‖	1.39	0.89	0.17	57
7	37	12	152	Basal		0.78	0.17	0.51	0.10	22	2.42	1.38	0.53	0.51	57
				Oatmeal	7.1	1.01	0.18	0.45	0.38	18	2.29	1.00	0.73	0.56	44
				Oatmeal	13.1	1.13	0.21	0.56	0.36	19	2.12	0.99	0.64	0.49	47
7	32	12	152	Basal		0.88	0.14	0.51	0.23	16	2.86	1.15	0.64	1.07	40
				Raw cabbage	2.8	0.99	0.14	0.54	0.31	14	2.67	1.25	0.96	0.46	47
				Raw cabbage	6.3	1.10	0.15	0.54	0.41	14	2.48	1.26	0.84	0.38	51
7	38	12	153.4	Basal		0.65	0.14	0.52	—0.01	22	2.46	1.32	0.87	0.27	54
				Peeled oranges	4.4	0.88	0.15	0.52	0.18	20	2.52	1.15	1.08	0.29	46
				Peeled oranges	9.7	0.97	0.20	0.73	0.04	21	2.60	1.10	1.39	0.11	42
7	38	12	155.2	Basal		1.38	0.18	0.43	0.77	13	2.40	1.42	0.86	0.12	59
				Peanuts	26.5	2.23	0.36	0.59	1.28	16	2.91	1.04	1.50	0.37	36
				Peanuts	33.1	2.83	0.45	1.15	1.23	16	3.23	1.15	2.00	0.08	36
7	39	12	155	Basal		1.38	0.18	0.43	0.77	13	2.40	1.42	0.86	0.12	59
				Raw carrot	2.7	1.36	0.17	0.56	0.63	13	2.68	1.25	1.01	0.42	47
				Raw carrot	6.5	1.35	0.22	0.50	0.63	16	2.84	1.13	0.72	0.99	40
8	38	13	144	Basal		1.38	0.17	0.41	0.80	12	2.40	1.23	1.12	0.05	51
				Raw carrot	2.7	1.36	0.22	0.55	0.59	16	2.68	1.01	0.83	0.84	38
				Raw carrot	6.5	1.35	0.24	0.72	0.39	18	2.84	1.13	0.94	0.77	40
9	31	10	144	Basal		0.80	0.16	0.37	0.27	20	2.88	1.39	0.62	0.87	48
				Raw carrot	2.6	0.82	0.11	0.18	0.53	13	2.47	1.19	0.31	0.97	48
				Raw carrot	5.4	0.88	0.14	0.28	0.46	16	2.16	1.14	0.70	0.32	53
10	19	7	113.2	Basal		0.90	0.17	0.32	0.41	19	1.89	0.90	0.65	0.34	48
				Cooked carrot	3.2	0.89	0.13	0.42	0.34	15	1.97	0.96	0.86	0.15	49
				Cooked carrot	5.8	0.94	0.13	0.60	0.21	14	1.77	0.86	1.22	—0.31	49
11	17	5	103.4	Basal		0.90	0.20	0.18	0.52	22	1.89	1.03	0.47	0.39	54
				Cooked carrot	3.2	0.89	0.16	0.27	0.46	18	1.97	0.90	0.39	0.70	46
				Cooked carrot	5.8	0.94	0.16	0.37	0.41	17	1.77	0.79	0.46	0.52	45
12	24	6	123.6	Basal		0.90	0.16	0.25	0.49	18	1.89	1.02	0.78	0.09	54
				Cooked carrot	3.2	0.89	0.13	0.31	0.45	15	1.97	1.13	0.93	—0.09	57
				Cooked carrot	5.8	0.94	0.14	0.44	0.36	15	1.77	0.83	0.98	—0.04	47
13	22	6	116	Basal		0.68	0.17	0.30	0.21	25	2.01	0.97	0.34	0.70	48
				Applesauce	8.1	0.58	0.15	0.27	0.16	26	2.02	1.02	0.53	0.47	50
				Applesauce	16.4	0.47	0.13	0.34	0.00	28	2.03	1.11	0.60	0.32	55
14	17	5	96.2	Basal		0.68	0.18	0.21	0.29	26	2.01	0.92	0.81	0.28	46
				Applesauce	8.1	0.58	0.15	0.21	0.22	26	2.02	0.96	0.64	0.42	48
				Applesauce	16.4	0.47	0.13	0.25	0.09	28	2.03	0.97	0.66	0.40	48
15	19	6	105.2	Basal		0.68	0.16	0.43	0.09	24	2.01	0.99	0.75	0.27	49
				Applesauce	8.1	0.58	0.13	0.29	0.16	22	2.02	0.97	0.68	0.37	48
				Applesauce	16.4	0.47‖	0.12	0.21	0.14	26	2.03‖	1.11	0.59	0.33	55
7	42	13	156.3	Basal		0.77	0.11	0.41	0.25	14	2.32	1.07	1.42	—0.17	46
				Roast pork **	6.9	1.03	0.20	0.30	0.53	19	2.49	1.17	0.91	0.41	47
				Roast pork **	12.4	1.16	0.23	0.31	0.62	20	2.71	1.04	0.82	0.85	38
4	25	8	126.6	Basal		0.53	0.10	0.29	0.14	19	2.13	0.97	1.17	—0.01	46
				Roast pork **	6.9	0.67	0.15	0.31	0.21	22	2.28	0.97	0.84	0.47	43
				Roast pork **	13.9	0.79	0.19	0.24	0.36	24	2.43	0.95	0.72	0.76	39
5	24	6	118.8	Basal		0.53	0.09	0.37	0.07	17	2.13	1.13	1.43	—0.43	53
				Roast pork **	6.9	0.67	0.15	0.25	0.27	22	2.28	1.04	0.96	0.28	46
				Roast pork **	13.9	0.79	0.22	0.40	0.17	18	2.43	1.03	0.91	0.49	42
16	23.9	9	130.5	Basal		1.25	0.15	0.41	0.69	12	1.21	0.75	0.92	—0.46	62
				Soybean **	7.6	1.25	0.25	0.29	0.71	20	1.19	0.72	1.04	—0.57	61
				Soybean **	14.9	1.26	0.19	0.45	0.63	15	1.18	0.49	0.98	—0.29	41
17	20.7	8	119	Basal		1.25	0.12	0.52	0.61	10	1.21	0.85	0.58	—0.22	70
				Soybean **	7.6	1.25	0.30	0.22	0.74	24	1.19	0.75	0.92	—0.48	63
				Soybean **	14.9	1.26	0.23	0.24	0.79	18	1.18	0.50	1.21	—0.53	42
18	22.3	6	114.4	Basal		0.83	0.05	0.35	0.44	6	0.80	0.75	0.62	—0.57	93
				Soybean **	7.6	0.84	0.15	0.38	0.31	18	0.80	0.54	0.62	—0.36	68
				Soybean **	14.9	0.84	0.11	0.26	0.48	13	0.79	0.40	0.56	—0.17	50
19	16	4	108	Basal		0.83	0.04	0.35	0.44	5	0.80	0.73	0.56	—0.49	91
				Soybean **	7.6	0.84	0.20	0.30	0.06	24	0.80	0.54	0.71	—0.45	68
				Soybean **	14.9	0.84	0.22	0.56	0.33	26	0.79	0.31	0.65	—0.17	39

* Per cent contributed by test food to total dry weight of diet (dried at 70 C in vacuo).
† U, urine; F, feces.
‡ I-TX intake minus total excretion; $\frac{UX100}{I}$, per cent of intake in urine.
‖ Refusals, intake not determined.
§ Enriched cornmeal.
¶ Common degerminated cornmeal.
# Whole white cornmeal.
** Feeding of the higher level of test food preceded the feeding of the lower level. The order has been changed for the Table to conform to that of the other studies.

sons showed changes under 10μg. from first three to last three days of the period, regardless of change in intake. These findings demonstrate that when intake is adequate, and changes are relatively small in comparison to the total intake, equilibrium is achieved quickly and after three days further changes in urinary excretion will be no greater than the variability expected from constant intake.

Similar review of urinary riboflavin excretion showed that small and irregular changes during all periods of collection were the rule; in no case were consistent deviations noted which could indicate lack of adjustment to the regimen. The purpose of the study was primarily to determine the urinary thiamine and riboflavin levels to be expected from healthy children ingesting mixed diets. We assume that these data may be considered as representative of the urinary excretion of thiamine and riboflavin to be expected from children given mixed diets varying moderately from time to time in content of these vitamins but approximating the intake values reported here.

Results

Table 1 lists the periods of study, the total calories, and distribution of calories for each subject; specimen diets are shown in Table 2. The detailed Table 3 contains average daily diet and urine and fecal data for each six-day period of the study. Figures 1 and 2 show the urinary excretion of thiamine in relation to intake. Diets for the low-thiamine studies are listed in Table 4; the data for these periods are reported as four-day means in Table 5, and the daily urine values are shown in Figures 3 and 4.

Thiamine.—For the statistical relationships, data for the low-thiamine studies were omitted, being considered as stress periods.

Eighty-four six-day studies of children given adequate intake of thiamine were available for statistical study. The daily thiamine intakes ranged from 0.46 to 2.83 mg. daily, the majority being between 0.6 and 1.4 mg. daily, with the mean value of 0.951 mg. These intake ranges are considered as customary for a considerable

TABLE 4.—*Diets* for Thiamine Depletion and Repletion†*

	Amt. Gm.	Cal.	Protein, Gm.	Fat, Gm.	CHO, Gm.	Thiamine, μg.	Riboflavin, μg.	Niacin, Mg.
Depletion diet								
Breakfast								
Milk	200	138	7.0	7.8	9.8	80	340	0.20
Soda crackers	16	68	1.6	1.6	11.5			
Toasted dry cereal	15	52	1.1	0.2	12.0	4		0.60
Butter	10	73	0.1	8.1				0.01
Sugar	10	40			10.0			
Peaches ‡	115	79	0.5	0.1	21.0	11	23	0.80
Egg white	60	28	6.4		0.5		160	0.06
Dinner								
Milk	100	69	3.5	3.9	4.9	40	170	0.10
Crackers	16	68	1.6	1.6	11.5			
Butter	10	73	0.1	8.1				0.01
Corned beef ‡	35	76	8.9	4.0		7	84	0.95
Beets ‡	35	14	0.4		3.0	3	11	0.03
Stick Candy	20	80			20.0			
Pears ‡	115	79	0.2	0.1	21.2	12	23	0.12
Marshmallows	15	52	0.4		15.0			
Sugar §	10	40			10.0			
Supper								
Milk	100	69	3.5	3.9	4.9	40	170	0.10
Crackers	16	68	1.6	1.6	11.5			
Butter	10	73	0.1	8.1				0.01
Cheese, cheddar	30	120	7.5	9.6	0.6	11	142	0.06
Carrots ‡	35	11	0.2	0.2	2.1	11	7	0.11
Stick candy	20	80			20.0			
Marshmallows	15	52	0.4		15.0			
Applesauce ‡	100	72	0.2	0.1	20.0	10	10	
Sugar §	10	40			10.0			
Evening lunch								
Milk	100	69	3.5	3.9	4.9	40	170	0.10
Cookie (Butterfinger)		304	6.1	12.0	45.0	60	80	
Total (estimated)		1,987	54.9	74.9	284.4	329	1,390	3.25
Total (analyzed)			53.5			326	1,399	
Diet changes for repletion period								
Added: ham	60	232	13.8	20.0		324	126	2.50
Deducted:								
Corned beef	35	81	8.5	4.0		7	67	
Stick candy, sugar	28	112			28.0			
Total (analyzed)			64.3			892	1,530	

* All diets were supplemented with 2 gm. of $CaHPO_4 \cdot 2H_2O$ and 25 mg. of niacinamide.
† Subject 20 had in addition 30 gm. cream and 12 crackers; total calories, 2,084. Subject 21 had in addition 30 gm. cream, 30 gm. dried apricots, and 12 crackers; total calories, 2,164. Estimated values are from Bowes and Church.[15]
‡ Canned.
§ Used in a synthetic drink.

TABLE 5.—*Thiamine and Riboflavin Excretion of Children During Depletion of Thiamine and During Recovery* *

Subject	Age, Yr.	Height, Cm.	Weight, Kg.	Thiamine					Riboflavin				
				Intake, μg./Day	Excretion		I–TX,‡ μg./Day	U×100,‡ I %	Intake, μg./Day	Excretion		I–TX, μg./Day	U×100, I %
					U,† μg./Day	F,† μg./Day				U, μg./Day	F, μg./Day		
16	9	132.4	24.6	326 §	31	319	−24	9.5	1,399	685	1,198	−484	48.9
			24.5	326	24	265	41	7.4	1,399	679	1,122	−402	48.5
			24.5	326	20 ‖	303	3	6.1	1,399	634	1,326	−561	45.3
			24.7	326	19	373	−66	5.8	1,399	806	969	−376	57.6
			24.8	892	67	398	427	7.5	1,530	724	1,591	−785	47.3
			25.2	892	96	528	268	10.8	1,530	834	1,020	−324	54.5
			25.4	892	118	281	493	13.2	1,530	672	765	93	43.9
			25.6	892	147	397	348	16.4	1,530	441	941	148	28.8
17	8½	120.0	21.3	326 §	48	269	9	15.0	1,399	772	714	−87	55.0
			21.4	326	33	221	72	10.0	1,399	748	814	−163	53.0
			21.5	326	30	329	−33	9.0	1,399	808	1,093	−502	58.0
			21.5	326	27	298	1	8.0	1,399	771	1,038	−410	55.0
			21.8	892	84	184	624	9.0	1,530	717	365	448	47.0
			21.8	841 ¶	111	315	415	13.0	1,506 ¶	989	796	−279	66.0
			22.1	892	122	246	524	14.0	1,530	860	618	52	56.0
			22.1	892	162	294	436	18.0	1,530	671	478	381	44.0
18	6½	116.0	23.1	326 §	30	340	−44	9.2	1,399	690	751	−42	49.3
			23.2	326	25	350	−49	7.7	1,399	736	734	−71	52.6
			23.4	326	20	414	−108	6.1	1,399	663	861	−125	47.4
			24.0	326	18	363	−45	5.5	1,399	567	789	43	40.5
			24.0	892	67	400	425	7.5	1,530	928	1,057	−455	60.6
			24.6	892	122	342	428	13.7	1,530	886	721	−77	57.9
			24.7	892	140	266	486	15.7	1,530	698	355	477	45.6
			24.7	892	163	451	278	18.3	1,530	532	1,109	−111	34.8
19	4¾	109.2	16.8	326 §	55	316	−45	16.9	1,399	753	1,109	−463	53.8
			16.7	326	36	265	25	11.0	1,399	603	612	184	43.1
			16.8	326	29	325	−28	8.9	1,399	586	792	21	41.9
			17.3	326	26	358	−58	8.0	1,399	733	816	−150	52.4
			17.4	892	79	347	466	8.9	1,530	710	903	−83	46.4
			17.4	892	151	390	351	16.9	1,530	821	677	32	53.7
			18.0	892	174	293	425	19.5	1,530	802	500	228	52.4
			18.4	892	198	305	389	22.2	1,530	697	1,426	−593	45.5
20	9	125.2	23.52	342 #	66	429	−153	19.0	1,446	476	1,005	−35	33.0
			23.50	342	34	566	−258	10.0	1,446	510	1,202	−266	35.0
			23.55	342	25	419	−102	7.0	1,446	564	1,079	−197	39.0
			23.95	342	17	303	22	5.0	1,446	711	1,360	−625	49.0
			23.65	954	53	556	345	6.0	1,785	647	884	254	36.0
			24.40	3,954 **	392	688	2,874	9.9	1,785	962	357	466	54.0
21	7½	128.6	26.4	345 #	55	158	132	16.0	1,496	686	803	7	48.0
			26.3	345	36	134	174	11.0	1,496	588	583	325	41.0
			26.2	345	24	--	--	7.0	1,496	642	--	--	45.0
			27.1	345	28	--	--	8.0	1,496	694	--	--	48.0
			26.5	345	12	--	--	4.0	1,496	590	--	--	41.0
			26.8	954	49	--	--	5.0	1,785	623	--	--	35.0
			27.0	954	82	107	765	9.0	1,785	672	723	390	38.0

* Data are averages of four-day periods of study.
† U, urine; F, feces.
‡ I-TX, intake minus total excretion; $\frac{U \times 100}{I}$, per cent intake in urine.
§ Supplemented with 2 gm. of $CaHPO_4 \cdot 2H_2O$ and 25 mg. of niacinamide daily.
‖ Complaints of leg cramps from 11th to 16th day.
¶ Refusals.
# 30 gm. of cream and 12 gm. of crackers added to low-thiamine diet.
** Supplemented with 3 mg. of thiamine plus 25 gm. of niacinamide.

segment of our child population. Benson [7] permitted children 4 to 10 years old to choose from hospital diets; he found most of the intake values between 0.9 and 1.00 mg. daily. Beal,[8] in a study of thiamine intake by Denver children up to 10 years of age, found 0.51, 0.74, and 0.95 mg. at the 10th, 50th, and 90th percentiles for 4-year olds, increasing to 0.75, 1.16, and 1.57 mg. for the same percentiles at 10 years of age.

The relation between the 24-hour intake and urinary excretion of thiamine is shown in Figure 1. The data for basal diets are shown as solid symbols; those for diets high in one food, as open symbols. The range of urinary thiamine observed from the basal diets does not differ from that of experimental diets containing the same amount of thiamine. The urinary thiamine values increased steadily with increase in the daily intake. The only exceptions were the data for intakes of less than 0.35 mg. daily, which have been omitted from the statistical analysis and will be discussed separately, and two studies of basal diets for the soybean group. For some reason for which we have no certain explanation, the four little girls of the soybean study excreted

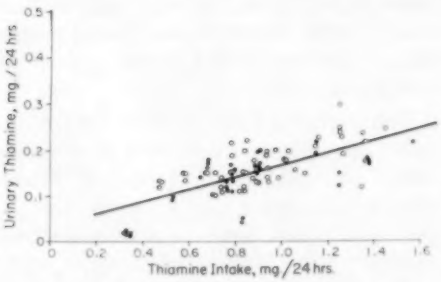

Fig. 1.—Daily urine thiamine in relation to daily intake. Solid dots represent periods of basal diet; circles show periods when experimental foods were given. The two highest values are not shown in this figure (see Fig. 2). The mean urinary values for the low-thiamine diets are shown here but were not included in the data for the regression equation.

very little thiamine during their basal period. The two younger girls excreted only 0.04 and 0.05 mg. daily. Although the total thiamine intake remained constant, urinary thiamine increased steadily for three of the four children when they were given the soybean diets (the higher level of soybeans was fed first) and for the fourth child remained constant at a level considerably above that of the basal period. One may speculate as to cause, but we have no certain explanation for the low thiamine excretion during the basal period. These children came from the orphanage which supplied the major part of our subjects, and physical examination on arrival at the hospital showed no evidence of illness.

The correlation coefficient between thiamine intake per 1000 Cal. and total urinary thiamine was only 0.46. Intake varied from 0.272 to 0.717 mg. per 1000 Cal. From 16% to 24% of the calories came from protein; 33% to 52%, from fat, and 29% to 50% from carbohydrates. It appears that, under the dietary conditions used, the total caloric intake is not a major influence on the urinary excretion of thiamine from a given intake.

A correlation coefficient of 0.77 was obtained between daily intake and urinary thiamine for the 84 studies—an excellent correlation and one that brings into question the importance of bacterial synthesis in the intestine as a source of thiamine for children living under these conditions of diet.

The 12-year old boy, Subject 7, was studied for 21 six-day periods with a range of thiamine intake from 0.65 to 2.83 mg.; his urinary thiamine values plotted against intake values were distributed about the mean in a manner (Fig. 2) similar to those for the group as a whole. The regression line of Figure 2 is that of Figure 1, determined for the group as a whole. The excellent correlation between intake and urinary excretion shown by this subject over a wide range of intake, which, however, was always adequate, again bears witness to the rapid adaptation of urinary excretion of thiamine to changes in intake if the child is not under stress.

As the various tissues of the body increase or decrease in size at different rates and body composition therefore changes with growth, data from children of considerable age range may not show the same intake-to-excretion relationship when compared on the daily and per kilogram daily bases. If a given nutrient is used predominantly by a specific tissue, its requirements will vary with the rate of growth of the specific tissue rather than with growth of the body as a whole. If the tissue is growing at a markedly different rate than the body as a whole, and the age range

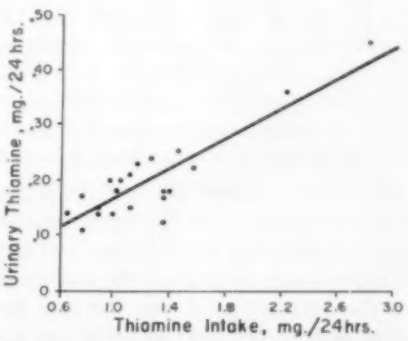

Fig. 2.—Daily urinary thiamine excretion of Subject 7 (12 years old) in relation to daily intake. The regression line is that of Figure 1, determined from the data of the entire group, and is extrapolated for the high-intake values.

studied covers notable changes in relative size of the given tissue, the relation of intake to excretion calculated on a per kilogram basis may differ considerably from that on a per diem basis. Therefore, a comparison of data in terms of total daily change with change per kilogram is a useful procedure in investigating requirements during growth.

When the data of Figure 1 were recalculated as milligrams per kilogram per 24-hours, a correlation coefficient of 0.71 was obtained between intake and urinary thiamine, again a good correlation, somewhat less marked than that on the daily basis.

The literature contains three reports of thiamine intake and urinary excretion of children wherein values can be calculated both as per diem and per kilogram. Two 5-year-old boys were studied by Oldham[9] at successively increasing thiamine intake levels, beginning with 150 mg. daily. Benson[7] studied 22 children 4 to 10 years old given diets whose thiamine content was estimated as approximately 1 mg. per day. Benson's second study[10] has not been included, as children excreting in the urine less than 20% of the intake were excluded as not normal. In the Widdowson-McCance-Holman studies[12] of German children 11 to 15 years old who had recovered approximately normal weight after malnutrition, thiamine intake was very high for the majority of the group, about one-half the total coming from dark bread. This high thiamine intake was considered characteristic of the orphanage diets for some years. Those subjects given unenriched or enriched white-flour bread had used this bread for about a year before the study was made.

Correlation between thiamine intake and urinary thiamine on a per diem basis for the 52 studies from the literature was 0.80; on a per kilogram basis, 0.69. Combining our data with those of the literature gave values of 0.77 per diem and 0.63 per kilogram. The evidence, as with our own data, points to the per diem basis as somewhat more valid; the differences between coefficients appear logical for substance, such as cocarboxylase, which is used by all tissues but in amounts graded to the activity of each tissue.

The percentage of thiamine intake excreted in urine is often used as a simple means of determining adequacy of intake. Benson[7] concluded that a normal child ingesting adequate amounts of thiamine will excrete 20% or more of the thiamine intake in the urine daily. Schondel,[13] in a study of Norwegian children, observed that children from 3 to 14 years of age excreted from 118μg. to 361μg. of thiamine daily. Diets for 29 of the older children were estimated to contain 58μg. per 100 Cal.; 15% to 28% of the intake was excreted, with a mean of 20%. When 44 normal children were given 2 mg. of thiamine by mouth, mean excretion was 16% of the intake, with a range of 3.8% to 47%. Few values, however, were under 10%.

The small boys studied by Oldham[9] excreted only 12% of a thiamine intake of 150 mg., the excretion rising to 29% and 32%, respectively, of intakes of 925 and 950 mg. The German children, whose intake varied from 0.97 to 2.28 mg. daily, excreted from 11% to 42% of the intake in the urine.

Urinary thiamine averaged 18.9% of intake for the 84 studies of our group where diets contained 0.46 to 2.83 mg. of thiamine, and the range of urinary thiamine varied from 5% to 28% of intake. Only the two little girls of the soybean study excreted less than 10% of intake.

Allibone and Finch[14] studied convalescent children who were up and about but who had recently recovered from febrile illness. With an average intake of thiamine (estimated) of 1.0 mg. daily, children 3 to 10 years of age excreted in the urine 12.6%, and children 10 to 13 years, 14% of the thiamine ingested.

Benson[10] observed that children with common colds excreted 25% or more of their thiamine intake in the urine, but for children with acute upper respiratory in-

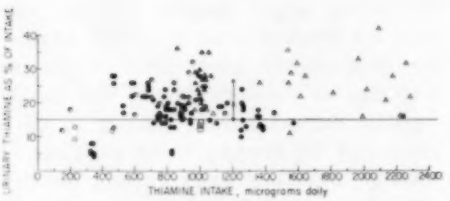

Fig. 3.—Urinary thiamine excretion of children 4 to 15 years of age as per cent of intake in relation to total daily intake. Solid dots represent data from this study; data from the literature are as follows: open triangles, studies of Holman[12]; solid triangles, those of Benson[7]; half-filled circles, those of Oldham.[8] The line and X at 1200μg. intake represent range and mean excretion of the children studied by Schondel,[18] and the large circles, the mean values of convalescent children of various age groups.[14]

fections urinary thiamine was 15% or less of the daily intake. Children in early convalescence also excreted less than 20% of the thiamine intake through the urine.

The urinary thiamine excretion as per cent of thiamine intake is shown for the studies in our group and those in the literature in Figure 3. Data from low-thiamine-intake periods are included. Schondel's mean intake value is empirically placed at 1200μg., and Allibone and Finch's at 1000μg. Obviously, a urinary thiamine of 20% of the intake is too high a minimum to include all healthy children. It can safely be said that the great majority of healthy children will excrete 15% or more of their thiamine intake in the urine. Values between 10% and 15% of intake may represent convalescence, mild illness, or low intake or may be normal for a given child. Values below 10% of intake certainly are cause for alarm, representing either too low an intake of thiamine or rapid destruction in the body.

Mickelson[15] has commented on the variability in thiamine excretion among individual subjects. Figure 3 bears out his findings, for at each adequate intake level a wide range is noted in per cent of intake excreted in urine. When the day's intake exceeded 1.5 mg. urinary thiamines varied from 11% to 44% of intake, but the majority exceeded 20%. These children had had a high thiamine intake for at least a year. At intake levels between 0.7 and 1.4 mg. daily, urinary excretion varied from 10% to 36% of intake, with the mean value approximating 20%. Habitually high intakes of thiamine seem to be accompanied by high percentage excretions in the urine; habitually moderate intakes result in a somewhat lower urinary thiamine.

For young women, Storvick et al.[16] considered an "excretion of 100 micrograms of thiamine per 24 hours, 13 per cent of the daily thiamine intake, and an excretion of 150 micrograms of thiamine per gram of urinary creatinine as indication of good nutrition in respect to thiamine." Of the children in our group, three excreted less than 100μg. of thiamine daily; the excretion of two of these has already been discussed; the third excreted 90μg. daily with an intake of 530μg. (pork basal, Table 4). One boy (carrot basal diet) and the four little girls given the basal diet for the soybean studies excreted less than 13% of their thiamine intake in urine.

Of the 84 studies, in only 3 was urinary thiamine less than 150μg. per gram of creatinine; the 12-year-old boy's second carrot study value was 112μg. per gram of creatinine, and the two smallest girls, whose thiamine excretion was inordinately low on the soybean basal diet, excreted 100μg. and 97μg. per gram of creatinine, respectively. Nine of the children at some time excreted amounts of thiamine between 150μg. and 250μg. per gram of creatinine; for the other 72 studies, urinary thiamine per gram of creatinine varied from 250μg. to 588μg. If urinary thiamine per gram of urinary creatinine is a guide to adequacy of diet,[17] these children had a luxus intake most of the time. The per cent of thiamine intake excreted in urine does not support such a conclusion. We must conclude that urinary thiamine per gram of creatinine is higher for children than for adults.

Thiamine Intake Below Requirement: Six of the children were given diets containing 0.326 or 0.345 mg. of thiamine daily. The diets were made otherwise ade-

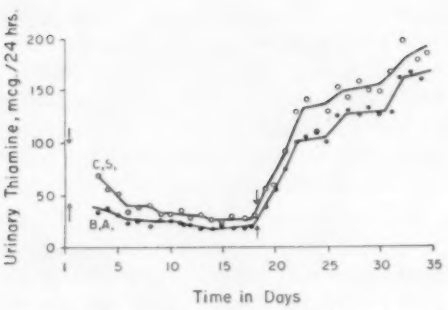

Fig. 4.—Urinary thiamine during depletion and repletion of thiamine. The arrows mark the interval of depletion, wherein the children ingested 326μg. of thiamine daily. The excretion values for Subjects 17 and 19 (open circles) have been averaged, as have those for Subjects 16 and 18 (black dots). Values for the two children of each pair were nearly identical. Note the stepwise decreases and increases in urinary thiamine.

quate according to the National Research Council Allowances by giving supplements of nicotinamide and dicalcium phosphate where necessary. The composition of the diets is given in Table 4.

Four of the children (Subjects 16, 17, 18, and 19) were studied as a group; these girls had been used as subjects for the study of utilization of soybeans. They were then given 0.326 mg. of thiamine daily; urine collection was started the third day. Urine values are shown daily (Fig. 4); urine and fecal excretion, in four-day averages (Table 5). The urinary excretion of thiamine dropped immediately from the high values of the preceding study. Subjects 16 and 18 excreted less than 40μg. daily on the third day of the diet; Subjects 17 and 19 needed five and six days, respectively, for the urinary thiamine to drop below 40μg. Because values for each pair were similar, though values for the two pairs differed, the mean daily excretion for each pair is shown in Figure 4. The minimum urinary thiamine observed was 14μg. (Subject 18, on the 15th day). Subjects 16 and 18, the two best able to conserve thiamine, excreted less than 20 μg. daily on four days out of the last seven. After the first sharp drop in urinary thiamine excretion of Subjects 17 and 19, all values appeared to decrease by stages, holding relatively constant for three or more days, then decreasing to a slightly lower level. From the 15th day to the 19th day of the dietary regimen, the eldest child, Subject 16, complained of leg cramps, which increased in severity; therefore the experiment was discontinued on the 20th day, by clinical advice. The mean urinary thiamine values for the 15th to 19th days were 18μg. and 26μg., respectively, for the two pairs. The two girls with the higher values, Subjects 17 and 19, were those whose urinary thiamines decreased more slowly at the beginning of the study. Subject 17 had consistently shown the highest urinary thiamine of the four taking the soybean diet which preceded this study; the urinary thiamine of Subject 19 during the soybean diet was more nearly comparable to that of Subject 16. Subjects 17 and 19 weighed less than the other two girls, though the weight difference between Subjects 18 and 17 is far less than that between Subjects 17 and 19. Neither weight nor age seemed to be a major factor in determining the rate of fall of urinary thiamine with decrease in intake.

With the moderate increase in dietary thiamine afforded by substituting ham for corned beef and omitting sufficient sugar from Diet 2 to make the two diets equicaloric, urinary thiamine increased promptly, so that the excretion of each child was 100μg. or more on the fourth day and continued to increase thereafter. The increase appeared to proceed in stepwise fashion; a sharp rise on one day, followed by two or three days of similar excretion, then a second sharp rise. Rate of increase was greater than had been the rate of decrease on institution of the low-thiamine diet. After seven days of the diet, Subjects 16 and 18 regularly excreted 100μg. or more. The other two girls evidently were not as depleted, for they maintained urinary thiamine of 150μg. or more from the fourth day on. Subject 19, the youngest, attained an excretion of 200μg. during the last 2

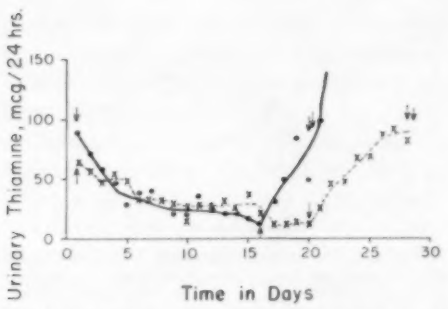

Fig. 5.—Urinary thiamine during depletion and repletion of thiamine. The single arrows mark the period of depletion; the double arrows indicate ingestion of therapeutic amounts of thiamine, after attempted repletion with a moderately rich diet. Black dots, Subject 20; X's, Subject 21.

days of the 16 which comprised this period, equalling her excretion during the soybean diet. Clinically, however, the children were all still markedly listless, and so large amounts of thiamine were given them for several days before their return to the orphanage. From the clinical observations, ability to maintain a level of urinary thiamine of 100μg. or above does not necessarily imply maximum metabolic utilization of the vitamin. The child who complained of severe leg cramps showed the slowest rate of rise of urinary thiamine.

The two children studied separately were given the diet fed the previous group plus some additional food (Table 4). The thiamine intake was 0.341 mg. daily. The data are shown in Figure 5. Subject 20, who was 9 years old, was given the low-thiamine diet for 16 days; her urinary thiamine excretion, though erratic, decreased more steadily than that of Subject 21 and dropped below 20μg. on the 15th and 16th days of the study. The thiamine intake was then increased, on clinical advice. The urinary thiamine of Subject 20 increased rather slowly the first four days of the recovery period. The child was then given 3 mg. of thiamine daily and achieved an excretion of 618μg. on the third day following introduction of the high-thiamine intake.

Subject 21, who was 7½ years old, was given the low-thiamine diet for 20 days. His urinary thiamine decreased rather slowly and in steps. During the last four days of the low intake, excretion dropped sharply from a level of 28μg. daily to 11μg. to 14μg. a day, with a mean of 12μg. The low-thiamine feeding was discontinued on clinical advice because the boy was so listless, and his thiamine intake was increased to 0.954 mg. daily. Urinary thiamine increased more slowly than for the first four subjects, and it had not reached 100μg. at the eighth day, when the diet was discontinued and the subject was given therapeutic doses of thiamine together with complete change of dietary regimen.

The six children all showed prompt conservation of thiamine with the low intake. Urinary thiamine excretion decreased to a mean of from 4% to 9% of the intake during the last eight days or more of the low-thiamine period, compared with excretion of about 19% during periods of adequate intake. Clinical signs of deficiency, especially listlessness, appeared early, and severer signs, such as leg cramps, were noted in one child soon after the urinary excretion decreased below 30μg. daily. With increased intake of thiamine, urinary excretion increased rapidly, but the clinical symptoms remained for some time after the urinary thiamine had attained the level observed with a normal diet. The listlessness observed early in the depletion period was sufficiently marked to cause comment and concern even by members of the medical staff who were unaware of the nature of the study. Only the one child complained of leg cramps.

The slow and stepwise changes noted in urinary thiamine and the length of time necessary for each child to reach equilibrium during depletion and repletion of thiamine are in sharp contrast to the relative constancy of excretion attained within four days in the nonstress periods of study. These findings are further evidence that metabolic adjustment under stress conditions is far more difficult of achievement than that under nonstress conditions.

Fecal Thiamine: Fecal excretion of thiamine, as would be expected, was more variable than urinary excretion. When 0.5 mg. of thiamine or more was ingested, the daily fecal excretion varied from 0.11 to 1.15 mg., the latter amount being excreted when the daily intake was 2.83 mg. Except for this one period of very high intake, fecal excretion appeared to bear little direct relation to intake. For example, Subject 7 excreted 0.5 to 0.55 mg. of fecal thiamine daily with intakes varying from 0.65 to 1.57 mg. daily; in other studies with similar intake range his daily fecal excretion might be as low as 0.3 mg. of thiamine (intake 1.03 mg., pork study) or as high as 0.73 mg. of thiamine (intake 1.97 mg., orange study). The difference between intake and excretion varied from −0.01 mg. in one study to a maximum of 1.60 mg. on the highest intake. In 10 studies, differences were from 0.70 to 0.79 mg. daily.

During the studies of very low thiamine intake, the fecal thiamine did not vary consistently in either direction. In neither the periods of adequate intake nor those of low intake do values for fecal excretion warrant the assumption of any demonstrable amount of absorption of thiamine synthesized by intestinal bacteria.

Riboflavin.—The data on riboflavin intake and excretion include those of the 84 six-day studies wherein the intake of both thiamine and riboflavin was considered adequate and also the riboflavin excretion of the six children studied for 45 four-day periods during thiamine depletion and repletion. The data are given in Tables 3 and 5, and the relationship between intake and retention on a per kilogram daily basis is shown in Figure 6. No marked differences are evident in the relative excretion of riboflavin in urine due to disturbed thiamine excretion. Neither is any evidence of conservation of riboflavin apparent from this Figure; more data with intake values below 50μg. per kilogram are necessary to establish such evidence.

The correlation coefficient between daily intake and urinary excretion of riboflavin is 0.85; between intake and urinary excretion in terms of milligrams per kilogram daily, 0.82. These coefficients, like those for thiamine, support the conclusion that both these vitamins, in the enzymes in which they occur, vary in quantity according to the activity of the separate tissues but are still a relatively constant proportion of body weight. Correlation between intake of riboflavin per 1000 Cal. and total daily urinary excretion was obviously so low that no statistical evaluation was attempted.

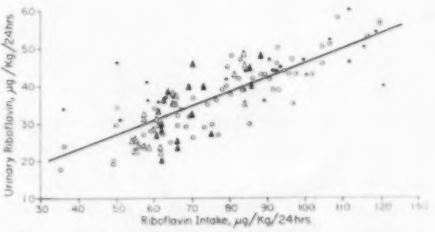

Fig. 6.—The urinary excretion of riboflavin in micrograms per kilogram per 24 hours, in relation to intake as micrograms per kilogram per 24 hours. Solid triangles refer to low-thiamine-intake studies; open triangles, to periods during recovery from low thiamine intake. The other symbols are as in Figure 1.

The correlation between daily intake and urinary excretion of riboflavin is sufficiently high to indicate that riboflavin produced by bacterial action in the gastrointestinal tract cannot be an important source of riboflavin for the child under the conditions reported here.

When the data were plotted as percentage of intake excreted in urine against age of the child, no consistent difference in relative excretion with age could be observed. Certain children seemed consistently to excrete a lower percentage of riboflavin intake than the mean for the group, but the differences usually were not marked. Aberrant values for urinary riboflavin were shown by the two children (Subjects 18 and 19) whose urinary thiamine excretion values were far below the range of the group during their basal period of study prior to soybean feeding. These two girls excreted in the urine 91% and 93% of the riboflavin ingested—a far higher percentage excretion

than shown in the second study of the same girls or by others with similar per kilogram intakes. Again, we have no explanation for these peculiar results.

Oldham [9] and Widdowson, McCance, and Holman [12] studied riboflavin as well as thiamine metabolism in their child subjects. Riboflavin intake of Oldham's two subjects began at 250 mg. daily and increased to 1450 mg. daily from food sources. The riboflavin intake of the German children was uniformly low, as only very small amounts of milk were included in the daily dietary. The German children thus presented the opposite situation to that of our group. Their thiamine intake was unusually high and that of riboflavin worrisomely low. In our group, thiamine intake was moderate; riboflavin intake, high. For Oldham's subjects, intake of the two vitamins was parallel. For the published data, correlation coefficients between riboflavin intake and urinary excretion were only 0.51; for the combined data of this study and the two published studies, 0.87. Correlation coefficients between riboflavin intake and urinary excretion per kilogram were, for the published data, 0.86; for the combined groups, 0.89. It seems obvious that intake is overwhelmingly the major factor in determining riboflavin excretion, as it is for thiamine.

Riboflavin intake and urinary excretion for all three groups are shown in Figure 7 on a milligram per kilogram daily basis. The lowest intake values for our group

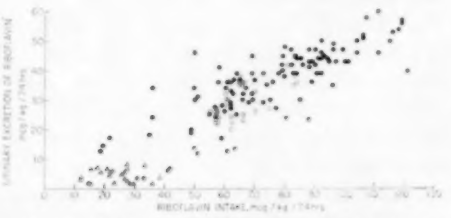

Fig. 7.—Urinary excretion of riboflavin in relation to intake, both measured on the basis of micrograms per kilogram per 24 hours. The open triangles show data from the Holman study,[12] and the half-filled circles, the Oldham study.[9] The black and open circles represent data from our study, the latter symbol representing studies with low thiamine intake or recovery from such stress.

were 35μg. and 36μg. per kilogram (0.79 and 0.80 mg. daily) for Subject 18 (soybean study) and 20μg. per kilogram for three children to be discussed subsequently. At 35μg. per kilogram daily, no clinical evidence of insufficiency was observed. This per kilogram intake was studied with only the one child for a period of one month. Her urinary excretion in this period showed no evidence of conservation, such as was observed at the lowest intake level of thiamine. In contrast, the riboflavin excretion of the German children, on a per kilogram basis, is in all cases less than that of the Iowa children. The low riboflavin excretion had raised the question of adequacy of intake by the authors of the report, a concern which we would share. The 5-year-olds studied by Oldham also excreted very little riboflavin when the intake was low. As the intake rose urinary excretion increased, but even at the highest intake urinary excretion was below that of our group. Apparently, when riboflavin intake is increased slowly from a low level urinary excretion of the vitamin lags for a time below that maintained by children accustomed to the higher intakes.

The effect of sudden and relatively large differences in vitamin intake on urinary excretion is illustrated by one of our own studies. Three of our own group, Subjects 4, 5, and 7, who were 8, 6, and 13 years old, respectively, were given a diet low both in thiamine and riboflavin at the conclusion of the pork study; the diet of Subject 7 was double that of the two smaller boys. Such a diet is difficult to plan, and our effort resulted in a diet low in protein, very high in carbohydrate, and unpalatable enough that it had to be discontinued at the end of nine days because of food refusals. Though the study cannot be considered at all definitive, because of its short duration and inconstant caloric ingestion, it seems worth reporting because of the contrasting behavior in urinary excretion of the two vitamins and because no study of children with low riboflavin intake immediately suc-

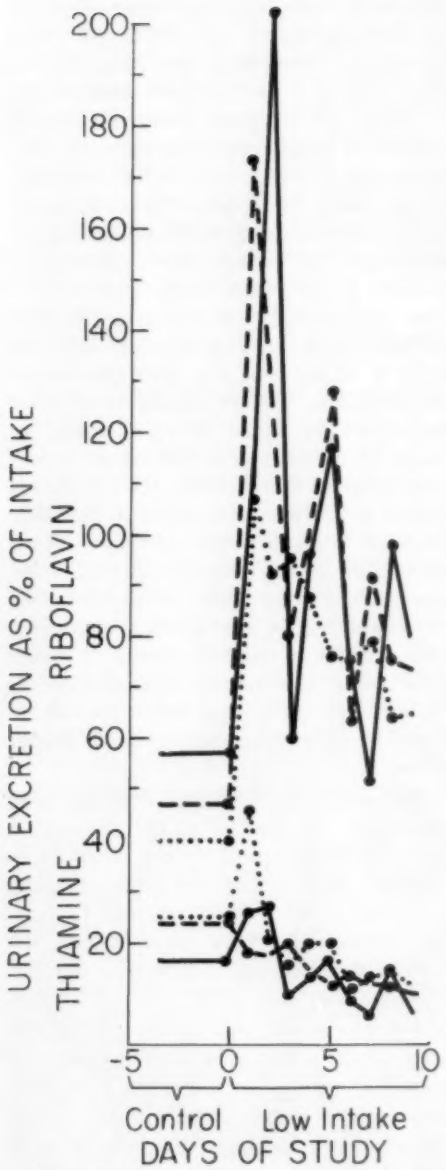

Fig. 8.—The per cent of intake of thiamine and of riboflavin excreted in urine. Intake levels for each child during the control and low-intake studies are given in Table 6. Dotted line, Subject 4; solid line, Subject 5; broken line, Subject 7.

ceeding habitual high intake could be found in the literature. The thiamine intake decreased from 25μg.-32μg. per kilogram to 10μg.-12μg. per kilogram, a decrease from moderate to low intake, like that of the more definitive study. Urinary thiamine decreased almost immediately, both in absolute amount and as per cent of intake (Fig. 8), as also had been observed with the other children. Riboflavin intake was cut from the high levels of 55μg.-101μg. per kilogram to approximately 20μg. per kilogram. In contrast to urinary thiamine, the urinary riboflavin excretion of Subjects 5 and 7 far exceeded 100% of the lowered riboflavin intake for several days, though the absolute excretion decreased; the excretion of Subject 4, though not as high, still decreased more slowly than did his thiamine excretion.

Although these children certainly had not reached their minimum excretion of riboflavin in nine days, the excretion of the last four days was roughly constant at from 12.5μg. to 17μg. per kilogram, whereas that of the German children, whose intake was similar but had been maintained for many months, held at between 5μg. and 8μg. per kilogram.

If the more carefully controlled data can be interpreted in the light of this crude study, it appears that the percentage of intake of a water-soluble vitamin which appears in the urine may depend not only on the intake at the moment but also on the customary level of intake—in other words, on the degree of storage of the vitamin. Thus the common interpretation of the need for long periods of adjustment to low intake holds for children as well as for adults. The relatively high excretion of riboflavin in relation to intake by the children of our group compared with those of the other studies and the higher thiamine excreted by the German children compared with the mean excretion of our own group point toward this conclusion. Benson's observation that children uniformly excreted a high percentage of thiamine intake in urine when the intake approximated the mean of our group may be interpreted as indicating that the children of his studies were accustomed to a somewhat higher thiamine intake.

TABLE 6.—*Urinary Excretion of Thiamine and Riboflavin by Subjects Given Low Intake of Both These Vitamins*

	Subject 5 (22.5 Kg.)		Subject 4 (23.2 Kg.)		Subject 7 (40.1 Kg.)	
	Thiamine	Riboflavin	Thiamine	Riboflavin	Thiamine	Riboflavin
Control period						
Intake, μg./day	750	2,280	750	2,280	1,000	2,490
Urine, 4-day mean, μg.	130	1,301	191	923	236	1,176
Depletion period						
Intake, μg./day	230	440	230	440	460	870
Urine, μg./day						
Day 1	59	479	105	763	84	935
Day 2	61	890	49	596	84	804
Day 3	23	264	36	350	87	828
Day 4	29	422	45	452	67	772
Day 5	38	515	45	566	56	674
Day 6	22	322	26	376	64	658
Day 7	14	233	31	353	56	799
Day 8	35	433	33	280	54	653
Day 9	17	360	28	283	50	640

Studies with normal young women [18] have indicated that urinary riboflavin varies inversely with the coexistent nitrogen balance. For children, retention of nitrogen is the normal condition and equilibrium or loss is abnormal. For the 84 studies of our group wherein nitrogen retention was determined, only 10 showed nitrogen loss, varying from 0.04 to 1.99 gm. daily, with a mean loss of 0.596 gm. daily. In these 10 studies, urinary riboflavin excretion varied from 0.75 to 1.39 mg. daily, averaging 1.071 mg. a day. For the 74 studies wherein nitrogen was retained, the mean retention was 1.089 gm.; mean urinary riboflavin, 0.971 mg. daily, with a range of 0.31 to 1.42 mg. daily; the majority of the urine values lie between 0.9 and 1.20 mg. per day. It appears that, in children, the changes in nitrogen retention noted here are without significant effect on the urinary excretion of riboflavin.

An excretion of 200μg. of riboflavin for each gram of creatinine in urine has been used as a measure of adequacy of riboflavin intake.[17] The children of our group, except when given an inadequate intake of riboflavin, excreted from 829μg. to 3382μg. per gram of creatinine, amounts which verify our conclusion that our group ingested ample amounts of riboflavin. Unfortunately, creatinine data are not available in the study of the German children,[12] but each of the four boys at Vohwinkel not given enriched bread excreted only 50μg. to 80μg. of riboflavin daily, averaging 70μg. As these boys were between 11 and 14 years old and weighed 79 to 98 lb., their urinary riboflavin most probably approximated 100μg. per gram of creatinine. Thus their low riboflavin excretion, always less than intake, may be considered evidence of conservation, and a habitual intake of riboflavin under 40μg., or perhaps even 50μg., per kilogram daily should be considered as below the safe level for a growing child.

Comment

The data both from our own study and from studies reported in the literature point strongly to the probability of storage of considerable amounts of both thiamine and riboflavin by children when intake permits. The relatively small increase in percentage of thiamine intake excreted in the urine of the German children (Fig. 3), whose habitual intake was high, compared with that of our group with a moderate but sufficient intake, points to the probability of storage of thiamine. The children of our group given low-thiamine diets obviously had little storage of the vitamin, though their previous daily intake had been adequate. The excretion of only 16% of 2 mg. of thiamine given to children by Schondel [13] shows that the Norwegian children also had relatively low storage of thiamine. The low excretion of thiamine by convalescent children can be explained on the basis of depletion of stores by illness and the resulting need of repletion.

The riboflavin data also point strongly to the probability of storage. Intake of our group was high; they habitually drank three or more glasses of milk daily. The German children had less than 100 cc. of milk daily and had had a low intake of riboflavin for years. Their urinary riboflavin values are far below the level of excretion of our group. The small boys studied by Oldham, given a low-riboflavin intake which was increased slowly and at intervals, excreted amounts of riboflavin in urine more comparable to those of the German children than to ours. Our three boys given low-riboflavin intake showed a much slower rate of decrease of urinary riboflavin than of urinary thiamine, which indicates that the relative amount of storage of riboflavin in our group far exceeded that of thiamine, as would be expected from their relative intake of the two vitamins.

In conclusion, it appears that a urinary excretion of thiamine maintained consistently at 20% or more of the thiamine intake and urinary riboflavin maintained consistently at 40% or more of intake may be considered as evidence that the intake of these vitamins is not only adequate but ample. A temporarily high percentage excretion of vitamin intake may be evidence only of a recent significant drop in intake. Urinary excretion of 15% to 20% of the thiamine intake and 20% to 40% of the riboflavin intake indicates adequacy of ingestion. A urinary excretion of less than 10% of intake of either thiamine or riboflavin is certainly cause for concern.

Summary

The thiamine excretion of children 4 to 13 years old who received from 0.326 to 2.83 mg. of thiamine daily in food has been studied. Thiamine intake was determined in each instance by analysis. No attempt was made to saturate the children with thiamine preceding the study.

The correlation coefficients between thiamine intake and urinary excretion, 0.77 on the per diem and 0.71 on the per kilogram basis, demonstrate that thiamine intake is the major factor influencing urinary thiamine excretion. Correlation of urinary thiamine with intake per 1000 Cal. was only 0.46.

Children receiving 0.7 to 1.4 mg. of thiamine daily excreted about 19% of the intake in the urine. Urinary excretion of thiamine per gram of creatinine appears to be higher for children than for adults.

Urinary riboflavin, like thiamine, varied directly with intake; the correlation coefficient was 0.85 on the daily basis and 0.82 per kilogram daily. These values show that riboflavin intake is the major factor regulating urinary excretion. No significant correlation between daily urinary riboflavin and intake per 1000 calories was observed.

No significant correlation was observed between urinary riboflavin and nitrogen retention; average urinary riboflavin excretion exceeded 800μg. per gram of creatinine.

The data from this study, together with those in the literature, are interpreted as evidence of storage of both thiamine and riboflavin in growing children given ample amounts of these vitamins. It is considered that a urinary thiamine excretion holding consistently at or above 20% of the intake and urinary riboflavin consistently above 40% of the intake are evidence that intake has been ample for some time. A urinary thiamine 15% or more of intake or urinary riboflavin 20% or more of intake is evidence of immediate adequacy of ingestion. Urinary excretion of less than 10% of the intake of either vitamin is considered cause for concern.

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Annular Pancreas Producing Duodenal Obstruction in the Newborn

Report of Three Cases

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Although annular pancreas is a congenital anomaly, it usually does not cause symptoms until adult life and may be found as an incidental autopsy finding. In a series of 58 cases collected by Giammattei,[1] in 1955, only 10 (17%) caused obstruction during the first 10 days of life. In 1954, Farringer[2] collected 14 cases in infants and children and added a 19-day-old case of his own. Because of the rarity of this condition as a cause of duodenal obstruction in the newborn, it was considered worth while to report three such cases seen by us during a two-month period.

The occurrence of annular pancreas can readily be related to its embryological development during the fourth week. Lecco's theory that adherence of the right ventral bud to its point of origin and its stretching to form an encircling piece of tissue at the time of rotation of the duodenum produces the annulus is the most widely accepted.[3] The theory of simple hypertrophy of both dorsal and ventral anlages to encircle the duodenum was promulgated by Tieken, cited by Kiesewetter.[4]

In contrast to the adult, in whom duodenal obstruction is rare and symptoms of annular pancreas are often vague and nonspecific epigastric distress, the most constant and dramatic symptom in the newborn is duodenal obstruction. In our cases the obstruction was complete. In the presence of such obstruction, vomiting occurs on the first or second day of life and continues thereafter. The vomitus usually contains bile, but this will vary with the location of the obstruction in relation to the ampulla of Vater.

The diagnosis of duodenal obstruction can frequently be made by simple x-ray examination of the abdomen. The presence of a gas-filled stomach and duodenum without evidence of gas elsewhere is diagnostic. Any infant who vomits during the first day or two of life should have the benefit of such examination if an early diagnosis is to be made. The differential diagnosis between annular pancreas and duodenal atresia will usually not be possible, but from a surgical standpoint it is of little importance. Further roentgenograms using a radiopaque substance may be desirable in some cases.

Suggested surgical treatment has been of two general types: resection of the annulus and the by-pass procedures. It would seem that the actual removal of the pancreatic tissue causing the obstruction would be the more reasonable, and in a number of cases such a procedure has been done. The results, however, have not been uniformly good. In a few the obstruction has not been completely relieved, and in others pancreatic or duodenal fistulae have resulted. Kiesewetter and Koop[4] reported a 43% occurrence of such fistulae in 14 patients treated by resection of the pancreatic ring.

The by-pass procedures have been generally more successful. The surgeon has the choice of gastroenterostomy, duodenoduodenostomy or duodenojejunostomy. Gastroenterostomy has the disadvantages of leaving

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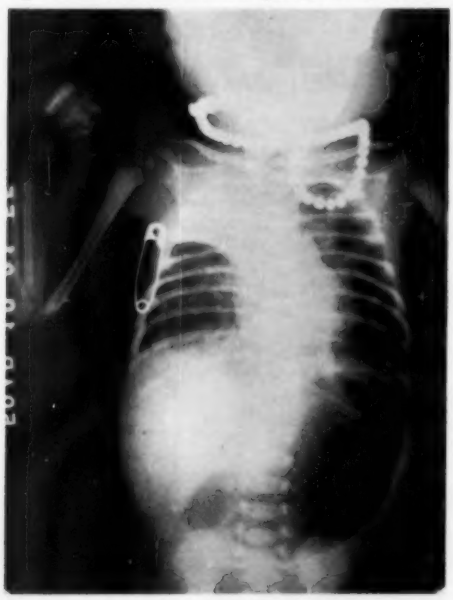
behind a blind duodenal loop which may cause symptoms and the risk of jejunal ulcer. In general, anastomosis of the dilated duodenum to the jejunum has yielded the best results. The occasional occurrence of duodenal atresia with annular pancreas would further increase the advantage of a by-pass procedure. Both conditions were present in one of our patients (Case 3). Additional congenital anomalies are found in 25% of annular pancreas cases.[3] One of our patients was a premature Mongolian idiot.

Report of Cases

CASE 1.—A 6 lb. 15 oz. full-term boy was born on Oct. 23, 1955. Delivery was spontaneous and uncomplicated. He began vomiting green fluid at 48 hours of age, and the abdomen was distended. A Levin tube emptied the stomach of bile-colored fluid, and the distention was somewhat relieved. He had a small meconium stool on the second, third, fourth, and fifth days of life and was noted to be jaundiced on the third day of life. He was unable to retain feedings and was maintained on parenteral fluids.

Surgical consultation was requested on the eighth day of life. A flat plate of the abdomen at this time (Fig. 1) showed the stomach and duodenum to be distended with gas, but no gas was demonstrated beyond the duodenum. A working diagnosis of duodenal obstruction was made, and surgery as soon as possible was advised. The abdomen at this time was moderately distended. No masses were palpated. The remaining physical examination was essentially nonrevealing with the exception of dehydration and a temperature of 103 F. Chest x-rays showed atelectasis of the right upper lobe. The patient was given further parenteral fluid replacement and was prepared for surgery.

Fig. 1 (Case 1).—Flat plate of abdomen, showing dilated stomach and first portion of duodenum.



Operation was performed on the ninth day of neonatal life, through a right vertical incision in the upper abdomen. There was free amber-colored fluid in the abdominal cavity. The stomach and first part of the duodenum were distended and edematous. The descending portion of the duodenum was mobilized. The midportion of the second part of the duodenum was seen to be obstructed by a ring of pancreas, completely encircling the duodenum at this site. The intestine distal to this point was collapsed and contained no gas. No other abnormalities were noted in the gastrointestinal tract or elsewhere in the abdomen.

A posterior duodenojejunostomy was performed with use of a two-layer anastomosis. The patient tolerated the procedure poorly. Postoperatively the patient did fairly well for two days. On the third postoperative day he had a period of apnea with sonorous rales in both lung fields. In spite of supportive therapy, he died on the third postoperative day.

Postmortem examination verified the diagnosis of annular pancreas, and there was a bilateral aspiration bronchopneumonia. The anastomatic site was patent and intact. No other congenital anomalies were found.

Comment.—Death in this case resulted from aspiration pneumonia and excessive loss of fluids and electrolytes. The surgical procedure was satisfactory, and had it been carried out before the pulmonary complications occurred it might have been successful.

The jaundice was presumably obstructive in nature and is not rare in such situations, as stated by Ravitch.[6]

Moore[5] reports that jaundice results from constriction of the common bile duct by the annular pancreas at the ampulla of Vater or an added factor of pressure on the common bile duct by the dilated first portion of the duodenum. The latter was thought to be true in the case here presented.

CASE 2.—A near-term boy was delivered by cesarean section. His birth weight was 7 lb. 6 oz.

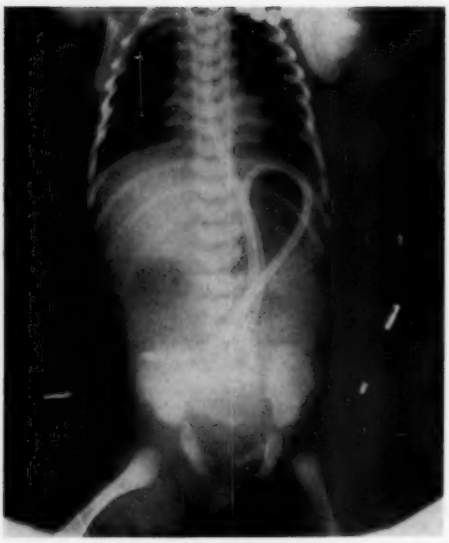


Fig. 2 (Case 2).—Flat plate of abdomen, showing dilated stomach and first portion of duodenum.

Fig. 3 (Case 2).—Photograph showing state of nutrition at 18 months of age.

The past history of the mother was of interest in that she had had one previous cesarean section, after prolonged labor, for cephalopelvic disproportion. Following the present cesarean section, a subtotal hysterectomy was performed for postpartum atonic uterus and partial placenta acreta.

The infant was noted to be distended at birth. He continued to be alternately distended and relaxed, after vomiting bile-stained mucus. No meconium was noted until early on the third day of life. The rectum was patent. There was a questionable left upper quadrant mass noted on the second day of life. Hydration was poor, and there was a 1 lb. weight loss in the first 48 hours of life. The infant was taking oral feedings poorly.

On the third day surgical consultation was obtained. A flat plate of the abdomen, at this time, revealed gas in the stomach and the first part of the duodenum (Fig. 2). Vomiting of bile-stained fluid continued. A working diagnosis of duodenal obstruction was made, and surgery was advised. Parenteral fluids were given, and the patient went to surgery on the same day.

An upper right rectus incision was made, and the abdominal cavity was opened. There was a small amount of clear intraperitoneal fluid noted.

The stomach was markedly distended, and there were several adhesions in the region of the gallbladder and duodenum, which were freed up with some difficulty. The first part of the duodenum was then visualized. It was dilated and markedly edematous. An obstruction, due to a constricting band of pancreatic tissue, extending around the entire circumference of the duodenum was noted in the midportion of the second part of the duodenum. Distal to this point, the duodenum and remaining small bowel were collapsed. Further examination revealed no other abnormality of the gastrointestinal tract. No attempt was made to dissect the pancreas from the duodenum. A posterior duodenojejunostomy was performed with

Fig. 4 (Case 2).—Barium study, showing excellent emptying through duodenojejunostomy 10 minutes after ingestion of barium. The obstructed area of the duodenum distal to the anastomosis can be seen.

a two-layer anastomosis. The patient's condition throughout the procedure was good.

The gastric tube was removed on the third postoperative day, and the patient was given small amounts of water orally. He regurgitated some of the orally administered fluid until the sixth postoperative day, when iodized oil (Lipiodol) x-ray studies showed the anastomosis to be functioning. Thereafter, recovery was rapid, and the patient was discharged on the 22d postoperative day. He was taking oral feedings well. Bowel movements were normal, and he was gaining weight. At 18 months, he is a healthy baby (Fig. 3). The adequacy of the duodenojejunostomy at this time is shown in Figure 4.

Comment.—A 3-day-old boy had complete duodenal obstruction due to an annular pancreas. Duodenojejunostomy gave complete relief.

CASE 3.—A white girl was delivered at 32 weeks' gestation. It was an uncomplicated breech delivery. Her birth weight was 3 lb. 10 oz. Mongoloid characteristics were noted at birth. The infant was placed in an incubator with oxygen immediately after birth. No oral feedings were given for the first 24 hours of life. Abdominal distention was noted the day following delivery. She was maintained by gavage feedings after 24 feedings, but it was noted that she regurgitated immediately on being placed on her abdomen. On the sixth day of life she suffered sudden respiration distress and died.

Postmortem examination reported Mongolism, prematurity, and duodenal stenosis with associated annular pancreas, which completely encircled the second portion of the duodenum. Section of the annular pancreas revealed normal pancreatic tissue. The stomach and the first part of the duodenum were markedly dilated. No other abnormality of the gastrointestinal tract was noted. There were numerous areas of pulmonary consolidation.

Comment.—Death in this case apparently resulted from aspiration bronchopneumonia, possibly secondary to unrelieved duodenal obstruction, although the presence of Mongolism and prematurity in itself has a high mortality. As in Case 1, early x-ray examination and proper surgical intervention might have relieved the obstruction.

Comment

The three cases reported illustrate the typical symptoms and radiological findings of duodenal obstruction due to annular pancreas in the newborn infant. The early onset of vomiting, especially of greenish fluid, should suggest the possibility of duodenal obstruction. The clinical abdominal distention and the radiological finding of a distended stomach and duodenum without evidence of gas distal to this point should establish the diagnosis. Annular pancreas as the etiology for the duodenal obstruction can rarely be diagnosed.

In the newborn with complete duodenal obstruction due to annular pancreas surgical intervention, during the first few days of life, is essential. The results of a by-pass operation, usually posterior duodenojejunostomy, have been far superior to those of direct attack on the annulus.

Summary

Three cases of annular pancreas in newborn infants seen during a two-month period are reported. In two cases the diagnosis was made at operation. In the third case diagnosis was made at autopsy.

Early diagnosis and surgical intervention are essential if the infant is to survive.

The by-pass operation (duodenojejunostomy) is the procedure of choice for this condition.

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Progress in Pediatrics

Acute Pancreatitis in Children

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Acute pancreatitis is known to occur most frequently in obese middle-aged men who have overindulged in food or alcoholic beverages. The onset is usually abrupt, with severe abdominal pain in the left epigastric region, nausea, and vomiting. The physical findings are often those of shock and signs of peritonitis. The serum amylase and urinary diastase values are elevated. When operation is performed, blood-stained fluid, also called "beef broth fluid," is found in moderate amounts. Fat necroses are present in the omentum, appendices epiploicae, or other adiposal tissues within the peritoneal cavity. The pancreas is usually enlarged and edematous; microscopically, more or less extensive areas of necrosis or hemorrhages are found to have replaced the normal pancreatic parenchyma.

In the pediatric age group this disease appears to be extremely rare. Blumenstock and co-workers [1] reported 4 cases and collected 36 cases from the literature. The observation of acute pancreatitis in a 4-year-old girl prompted the review of all original reports of this disease in children, with the intention of investigating its etiology and clinical course. Including our own patient, we found 38 cases, 7 of them caused by trauma, 1 most likely by trichobezoar, 2 possibly by ascarides, and 3 possibly as a result of prolonged administration of steroid hormone. Only one case may have been a manifestation of mumps. In some of the remaining 24 patients, only hypotheses regarding the etiology were offered. Several of the cases included in the review of Blumenstock and co-workers could not be clearly classified as acute pancreatitis. The statement often found in the literature that acute pancreatitis occurs in children frequently after mumps, scarlet fever, diphtheria, typhoid fever, and influenza could not be verified.

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Report of a Case

A 3 10/12-year-old girl was admitted to the U. S. Army Hospital in Munich, Germany, because of abdominal pain, vomiting, and fever of 24 hours' duration.

Eighteen days before the patient was seen she complained of a sore throat and had a fever, with temperatures ranging from 102 to 103 F; the leukocytes numbered 14,700. No treatment was given, and her temperature became normal within two days. However, one day later she again developed fever; she was thought to have a relapse of her tonsillitis and was treated with chlortetracycline. On the sixth day of therapy she developed urticaria on the abdomen and legs and her temperature rose to 104 F. Chlortetracycline was discontinued, and diphenhydramine (Benadryl) was administered in a dosage of 15 mg. four times a day. Urticarial eruptions were noted the next day over the joints. In three days the patient's temperature became normal and her skin cleared.

Two days before the patient was seen in our hospital she began to complain of vague abdominal pain. During the early morning hours of the next day she awoke with a sudden, severe pain in her abdomen and began to vomit. She was treated in a U. S. Army dispensary for gastritis with a mixture containing camphorated opium tincture (paregoric) and bismuth. However, her pain and vomiting continued, and when she was seen six hours before admission her temperature was 101.0 F and her leukocytes numbered 12,000. She

was referred to our hospital with the presumptive diagnosis of acute appendicitis.

Her past history was entirely negative. No history of contact with mumps could be elicited, and no cases of that disease were reported from the area of her residency at that time. The patient's maternal grandmother, her mother (37 years old), and a sister (7 years old) all have recurrent episodes of unexplained abdominal pain.

On examination, the patient complained of slight abdominal pain; her temperature was normal, and the pulse rate was 90 per minute. The abdomen was somewhat distended, and she had slight tenderness in the epigastrium. The bowel sounds appeared to be increased. Her leukocyte count was 22,100, with 3% juvenile forms and 85% neutrophils, and her hemoglobin was 15 gm. A culture of a catheterized urine specimen remained sterile.

An x-ray of the chest failed to show any abnormality. A flat plate of the abdomen revealed dilatation of both the small and the large bowel, which was interpreted as a sign of early adynamic ileus.

During the next few hours the patient complained of increasing abdominal pain and her temperature rose to 100.8 F rectally. A little later she began to cry continuously because of pain and her abdomen became more distended. On examination there was muscle rigidity in the right lower quadrant and no bowel sounds were audible. It was believed that the patient had an "acute abdomen," possibly appendicitis with perforation or bowel obstruction of unknown etiology, and it was decided to perform a laparotomy.

Approximately 300 cc. of a clear brownish fluid was found. The entire intestine, including the large bowel, was found to be distended. On the omentum and adiposal tissues of the bowel, small yellowish plaques were noted, which were markedly concentrated in the upper part of the abdomen, especially about the first part of the duodenum. Biopsy specimens were taken from the omentum including four of these plaques, which were later shown to be areas of fat necrosis with amorphous calcifications and infiltration by neutrophils and lymphocytes. The pancreas was examined, but no abnormal enlargement was noted. A culture of the peritoneal fluid remained sterile, but the amylase level in the peritoneal fluid was 375 Somogyi units (normal, 80 to 150 units). On the basis of these findings, the diagnosis of acute pancreatitis was made.

Postoperatively, a suction tube was placed in the stomach and fluids were administered parenterally. She was also given a combination of penicillin and streptomycin, atropine sulfate in a dose of 0.1 mg. four times daily, and a transfusion of 125 cc. of whole blood. Her condition improved steadily; on the 5th postoperative day the gastric suction tube was removed, and on the 13th day the patient was dismissed.

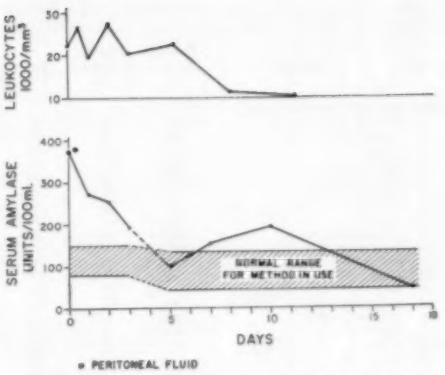

Fig. 1.—Serum amylase values and leukocyte counts during the course of acute pancreatitis.

In Figure 1 are given the serum amylase values and the leukocyte counts throughout her illness. For the first four serum amylase determinations the method described by Somogyi was employed, and for the last four examinations the method described by Smith and Roe was utilized by our laboratory. Serum electrolytes and, specifically, serum calcium levels were repeatedly examined and found to be within normal limits. The blood sugar was normal, and no sugar was excreted in the urine. On the 10th day of her illness a complement-fixation test for mumps was found to be negative with a titer of 1:8.

Seventeen days after the surgical intervention the patient was readmitted because of slight abdominal pain and one episode of vomiting. Her temperature was 101.4 F six hours before examination, but when she was examined there was no elevation of temperature and no evidence of pathology was found. The serum amylase value was normal. X-ray examinations of the stomach and duodenum were within normal limits. No parasites or ova or occult blood was present in several of the examined stool specimens.

The patient was to be seen again in order to obtain a blood specimen for a second complement-fixation test for mumps, but she failed to keep the appointment.

Review of the Literature (Table)

So-Called Idiopathic Cases.—Twenty-four records from the literature were reviewed. The findings of our own patient are included. Pancreatitis without definitely known etiology occurred twice as frequently in females as in males. The youngest pa-

Reported Cases of Acute Pancreatitis in Children

Case	Author	Year of Report	Age of Patient, Yr.	Sex
Cases without known etiology				
1	Phélip [2]	1920	7	F
2	Anderson [3]	1923	4	F
3	Vogel [4]	1924	13	F
4	Sebening [5]	1925	13	F
5	Holzmann [6]	1927	3	M
6	Mackenzie [7]	1930	3	F
7	Covaro [8]	1931	13	F
8	Foged [9]	1932	11	F
9	Desjacques [10]	1932	5	M
10	Dobbs [11]	1935	12 ½	F
11	Sujoy [12]	1936	8	F
12	Arana [13]	1940	6	F
13	Jaeger [14]	1943	4	F
14	Anavitarte [15]	1945	11	M
15	Dey [16]	1951	1 10/12	F
16	Ger [17]	1954	3	F
17	Boss [18]	1955	6	M
18	Haigh [19]	1956	4	F
19	Haigh [19]	1956	4 ½	M
20	Gibson [20]	1956	6	M
21	Pender [21]	1957	3	F
22	Blumenstock [1]	1957	⅗	M
23	Blumenstock [1]	1957	1 ¼	F
24	Blumenstock [1]	1957	6	M
Cases associated with Ascaris infestation				
1	Gallie [22]	1924	2 ½	M
2	Herzog [23]	1929	2	F
Case presumably due to trichobezoar				
1	Singer [24]	1952	13	F
Cases due to trauma				
1	Dobrotvorsky [25]	1912	12	F
2	Hagedorn [26]	1913	7	M
3	Dietrich [27]	1914	6	M
4	Liedberg [28]	1937	11	F
5	Kastrup [29]	1938	12	M
6	Adams [30]	1939	7	M
7	Shallow [31]	1947	8	M
Cases occurring after prolonged administration of steroid hormones				
1	Baar [32]	1957	11	F
2	Baar [32]	1957	3	M
3	Marczynska-Robowska [33]	1957	5	M

tient reportedly suffering from pancreatitis was 8 months old, and, in this review, three 13-year-old patients are included. No indication of a hereditary factor was found. The past history was not recorded from seven patients. Twelve patients had various contagious diseases typical for the pediatric age group. Patient 10 had erythema nodosum at the age of 9 years and again two months before the onset of the acute illness. Patient 13 had ascarides on a previous occasion, but there were no ascarides found at autopsy, death having resulted from pancreatitis. Three patients reported by different authors lived in mental institutions (Patients 6, 13, and 14); Patient 6, because of "congenital idiocy."

Only one patient (Case 10) had had mumps previously; the sister of Patient 15 had mumps during the patient's acute illness. In eight cases the reports clearly indicate no known exposure to mumps.

The immediate preceding history was possibly significant in 11 patients, while the disease occurred suddenly, in children who had apparent good health, in 5 instances. In three patients episodes of intermittent abdominal pain were present (Cases 8, 16, and 17). Patient 21 had had an episode of abdominal pain and vomiting at the age of 2 years. In Patient 19 poor appetite and pallor were noted for three weeks and constipation for four days prior to the onset of the disease. Patient 17 had, at the age of 3 years, jaundice, pale stools, and dark urine; presumably this represented infectious hepatitis. Later he had occasional abdominal pain and anorexia. Four weeks before the onset of the acute symptoms he was said to have pneumonia, and four days before the acute pancreatitis was diagnosed he again developed jaundice, had pale stools, and developed dark urine.

Our patient had a febrile illness 18 days before we saw her and acute tonsillitis four days later. Patient 4 had tonsillitis 12 days before she began to have symptoms of acute pancreatitis. Patient 10 had had otitis media with perforation two months previously, and a streptococcal brain abscess was drained 12 days before her acute illness. Patient 20 had a febrile illness with earache, sore throat, and fever one month and purulent otitis media with perforation one week before he was hospitalized because of acute pancreatitis. Patient 21 had acute tonsillitis caused by β-hemolytic streptococci at the time she was admitted with abdominal symptoms leading to surgical exploration.

Another interesting feature in our patient was the severe urticaria following her episode of tonsillitis and the administration of chlortetracycline. The urticaria lasted four days and had cleared five days before she was operated upon.

All reports which were sufficiently detailed emphasize that the onset of symptoms of acute pancreatitis is very sudden, and, in the majority of cases, the parents were

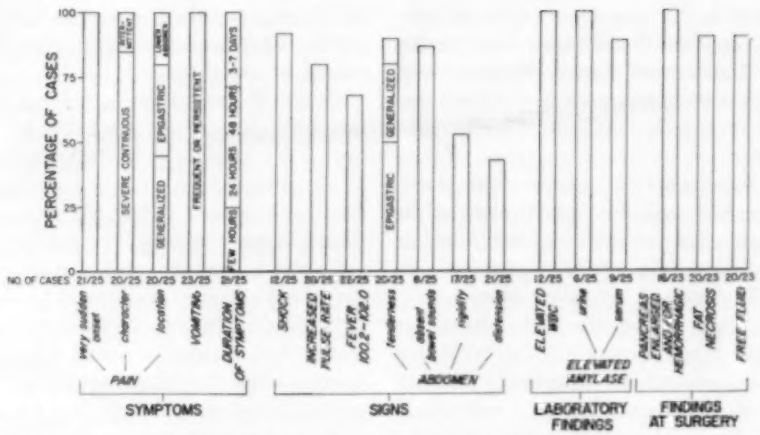

Fig. 2.—Symptoms, signs, and laboratory and surgical findings in "idiopathic pancreatitis." Percentage is derived from the total number of cases in which information was available (figures are given at the bottom of each column).

able to give the exact time of onset (Fig. 2). The abdominal pain was usually described as being severe and generalized. When the children were able to localize the pain, the maximum intensity was described to be in the epigastric region. The abdominal pain was in all cases associated with severe vomiting, which was described as being frequent, persistent, or continuous. The symptoms in most of these children were usually severe enough to cause the parents to seek medical attention within the first 48 hours.

The majority of patients had slightly elevated temperatures, averaging 101 F, and usually the pulse rate was elevated. Similar to the findings in adult patients, there were clinical signs of shock in 10 instances.

The abdominal findings were in most patients interpreted as evidence of peritonitis. When recorded, the bowel sounds were usually stated to be absent. Abdominal distention was specifically mentioned in eight instances. The more detailed reports usually describe generalized or epigastric tenderness, and in eight patients abdominal rigidity is reported. None of these patients had any physical findings suggestive of mumps parotitis.

X-ray examination of the abdomen was done in four cases. Two films were described as normal. In Patient 15 and in our patient, distention of loops of small and large bowel was described.

When determined, serum amylase values were elevated and the excretion of diastase in the urine was found to be increased. In our own patient the peritoneal fluid had a high amylase content at the time of operation.

Blood cell counts were reported in 12 patients, revealing marked leukocytosis, with counts ranging from 8100 to 49,000 and with a mean of 23,600. Blood sugar values were determined in three patients; only in Patient 18 was the value initially high (232 mg/100 ml.). It was found to be normal after recovery from the acute illness. In the same case, acetone and sugar were present in the urine during the acute stage. In nine other patients no abnormal urinary findings were reported. In only two patients was the stool tested for ova and parasites, and results were negative. Mumps titers during the acute phase were normal in three patients; in Patient 20 mumps titer was 1:40. No determinations during convalescence were reported.

Twenty-three patients underwent laparotomy; two patients died before the procedure could be carried out. Only in Patients 17 and 23 was the possibility considered that

the clinical picture represented acute pancreatitis, and in these cases high serum amylase levels were found preoperatively. The preoperative diagnosis in the other patients was usually that of a perforated appendix.

In the majority of patients free blood-stained or brownish fluid was present in the peritoneal space in amounts described as considerable, large, or even massive. In Patient 17 the fluid was bile-stained.

Three authors described the bowel as distended. Fat necroses of the omentum, mesentery, appendices epiploicae, and the capsule of the pancreas were present in almost all cases. Their nature was confirmed by biopsy in five instances. The pancreas was found to be enlarged and/or hemorrhagic when inspected. In Patient 23 marked necrosis of the tail of the pancreas was present in addition to a pseudocyst.

The biliary tract was usually described as being normal, but in Patient 4 a pea-sized gallstone was found in the papilla of Vater. In Patient 5 a common opening of the common duct and the pancreatic duct was present.

Of these 25 patients, 10 died, 8 after surgery. The diagnosis was verified by autopsy in all of these 10 cases. Microscopically, large areas of necrosis and hemorrhage were present in the pancreas. It should be noted that both patients who died after 1932 had fatty degeneration of the liver.

In most of the patients who recovered from acute pancreatitis, the therapy followed closely the treatment of acute pancreatitis in adults, consisting primarily in the administration of parenteral fluids and blood for the treatment of shock, the institution of gastric suction, and injection of atropine or propantheline (Pro-Banthine). In a number of cases, antibiotics were given.

Cases Associated with Ascaris Infestation.

In adults it has been reported that ascarides may cause acute pancreatitis by blocking the pancreatic duct. Schmieden and Sebening [34] mentioned that 50 of these cases were reported in the literature. In the pediatric age group there were two instances in which the pancreatitis was thought to be caused by ascarides.

Patient 1 had a mild episode of influenza one week before the acute illness, but Patient 2 was thought to be healthy. The onset of the disease was in both cases very sudden, with severe abdominal pain and repeated severe vomiting. No detailed physical examination was reported, but in Patient 1 the whole abdomen was found to be tender, with rigidity in the right upper quadrant, and he had a leukocyte count of 15,000. At operation the peritoneal cavity was found to contain blood-stained fluid, and fat necroses were present in the omentum and the capsule of the pancreas. The pancreas itself was found to be firm and swollen. This patient vomited an Ascaris 15 hours after the operation and recovered.

The second patient died 22 hours after onset of the acute symptoms. An Ascaris was found in the terminal vomitus. The autopsy revealed fat necroses on the adiposal tissues of the peritoneal cavity. The pancreas was almost completely necrotic, containing hemorrhagic areas.

Case Due to Trichobezoar.—Singer,[24] in 1952, reported the case history of a 13¼-year-old girl who had been known to chew and actually swallow hair for a number of years. She injured her upper abdomen by falling against the edge of a bench. Two days later she suddenly began to have abdominal pain and vomiting. Another two days later she was acutely ill, with a pulse rate of 120, a temperature of 101 F, and generalized abdominal tenderness and rigidity. After the abdomen was opened, a large amount of serous fluid escaped. The transverse colon was distended, while the omentum and the appendices epiploicae were covered with fat necrosis. A large tumor was found which was adherent to the posterior wall of the stomach. Serum amylase and urinary diastase were elevated. Three months later a cyst of the pancreas was aspirated, and 40 cc. of fluid was obtained. After another three months, the patient was readmitted with signs of intestinal obstruc-

tion and a trichobezoar with a weight of 420 gm., filling the stomach, duodenum, and upper part of the jejunum, was removed. The patient died on the following day.

Pancreatitis Following Trauma.—Seven patients in whom trauma to the upper abdomen was supposedly the cause of acute pancreatitis were reported in the pediatric age group. Three of them fell from a bicycle, striking the upper abdomen with a handle bar; one child was kicked in the abdomen; one was run against a barrier, and two were run over by a cart. The interval between trauma and the onset of symptoms was usually 24 to 72 hours; in one patient, just a few hours, and in two, 9 to 10 days.

The physical findings were very similar to those reported in the group of cases in which the etiology was unknown. The temperature was usually normal, but the pulse rate was elevated. The abdominal findings were those of peritonitis.

Serum amylase determinations were carried out in two patients and found to be elevated. The urinary diastase was reported to be high in one of these two cases and in a third case. Two patients had transient glycosuria; one, transient acetonuria. Leukocyte counts were reported in only two patients, and in both they were 18,000. All seven patients were operated upon. Blood-stained or brownish fluid was found in five. Only one report mentions distention of the bowel. Fat necroses were present in all seven cases, usually on omentum, mesentery, and capsule of the pancreas. The pancreas appeared to be grossly normal in three cases, but in Patient 5 it appeared edematous and partly necrotic and in Patient 3 a cystic swelling containing fluid was found. In Patient 4 a hematoma was observed in the region of the head of the pancreas. All patients recovered.

Pancreas Necrosis During the Course of Steroid Hormone Therapy.—Most recently, the case histories and findings at autopsy of three children dying suddenly after they had received a prolonged course of steroid hormones were reported. One was a 3-year-old boy suffering from dermatomyositis who had received steroid hormones for seven months. A 5-year-old girl had been treated because of rheumatoid arthritis for four months with corticotropic hormone when she died suddenly. The third patient was a 16-year-old girl suffering from severe asthma who had been receiving cortisone for five months before she died.

The clinical course did not quite follow the typical pattern described for acute pancreatitis; all these patients died very suddenly. All three were found to have extensive necrosis of the pancreas and fat necroses in the immediate surrounding tissue.

Comment

The review of all cases of pancreatitis occurring in the pediatric age group was of little help in the search for specific etiologic factors except in the seven cases in which trauma to the upper abdomen appeared to be the definite cause. In Schmieden and Sebening's [34] group of 2137 adult cases, 62 were supposedly due to trauma. The case in which a huge trichobezoar was found was probably in part due to a preceding injury. Only one patient was reported in whom a gallstone was found to be impacted in the papilla of Vater. The two cases in which an Ascaris was found may have been due to obstruction of the pancreatic duct by an Ascaris, but this is hardly more than an assumption, since in both cases the ascarides were found after vomiting. Novis [35] has reported the case of a 12-year-old girl in which two ascarides had blocked the pancreatic duct, but her clinical picture course could not be called typical of acute pancreatitis.

The question of how often the mumps virus causes acute pancreatitis with a "surgical abdomen" cannot be answered. In only 1 of the 30 nontraumatic cases was exposure to mumps recorded, and none of these was observed to have other clinical manifestations of mumps. Patient 20 had a mumps

titer of 1:40 during the acute phase, and this was probably due to a previous episode of mumps. In our own patient, Patient 21, and Patient 24, the complement-fixation titer for mumps was low during the acute phase. Zelman [36] reported that, among 89 patients suffering from mumps, serum amylase and urinary diastase values were raised in 73%, and 93% of 13 patients with clinical pancreatitis had increased amylase values. Applebaum [37] found elevated serum levels in 85% of 60 cases of mumps.

In Paxton's [38] series of 307 cases of acute pancreatitis, only 1 case was probably due to mumps. Schmieden and Sebening's [34] report included no case due to mumps. Eagles' [39] series of 1664 servicemen suffering from mumps included only 3 cases of pancreatitis. The diagnosis was based on clinical observations only. It appears that pancreatitis due to mumps is usually not severe and does not cause a "surgical abdomen."

Five patients had a purulent infection 7 to 15 days before the onset of their acute pancreatitis; this was proven to be due to Streptococcus in three instances. Hypothetically, the pancreatitis may have been caused directly by the Streptococcus, but no suppuration was reported and the peritoneal fluid was sterile in two of these patients. There is the other possibility that an antigen-antibody reaction takes place in this disease. Thal and Brackney [40] were able to produce acute hemorrhagic necrosis of the pancreas in rabbits and goats by the local Shwartzman reaction. The animals developed hemorrhagic pancreas necrosis after introduction of the endotoxin of meningococci and Escherichia coli into the pancreatic duct followed by an intravenous injection of the same toxins. Thal [41] also observed the development of severe hemorrhagic pancreatitis in rabbits after they were sensitized to egg albumin and had subsequent infusions of very small amounts of the same material into the pancreatic duct. This seems to represent an Arthus sensitization reaction.

Our patient developed urticaria nine days before admission. This would seem to give support to the hypothesis that a hypersensitivity reaction may be involved in the pathogenesis of acute pancreatitis.

It is impossible to state whether the administration of steroid hormone was the immediate cause of the necroses of the pancreas in the three patients reported. The fact that pancreas necrosis occurred in patients suffering from diseases often considered to be manifestations of an ill-defined hypersensitivity reaction might also add support to the thesis that pancreatitis in children belongs to the same group of diseases.

In the years since adequate postoperative fluid therapy has been used, the majority of children have survived; only two fatalities in children have been reported since 1932. The maintenance of adequate fluid and electrolyte balance may be an important point in postoperative treatment. Of course, all suggestions concerning the therapy of pancreatitis in adults seem to be applicable to the disease in children, including gastric suction and administration of atropine or propantheline to suppress reflex secretion of pancreatic juice. Adequate sedation and possibly administration of antibiotics are also standard treatment for adult patients with acute pancreatitis.

Awareness that acute pancreatitis may occur in children should prompt more frequent serum amylase determinations in children with acute abdominal findings. This might help to avoid occasional unnecessary laparotomies in cases of pancreatitis, especially following abdominal trauma.

Summary

A case of acute pancreatitis in a 4-year-old girl is reported. Thirty-seven other cases of acute pancreatitis occurring in the pediatric age group were found in the literature. Seven of them were caused by trauma; one, by trichobezoar; two, possibly by ascarides, and three, during steroid hormone treatment; one was conceivably due to

mumps. The etiology of the other 24 cases remained obscure.

The clinical course of this disease in children, regardless of the possibly different etiologies, was found to be very typical, with a sudden onset of abdominal pain and vomiting, all the signs of an acute abdomen, marked leukocytosis and elevated serum amylase levels, and, at surgery, blood-stained peritoneal fluid, multiple fat necroses, and enlargement and edema of the pancreas.

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Case Reports

Eosinophilic Granuloma

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In a recent review of patients treated for reticuloendotheliosis of the nonlipid type, the author [1] made note of the apparent increase in frequency of this condition. Our experience at the Children's Memoral Hospital with patients of the Letterer-Siwe and Hand-Schüller-Christian group shows these conditions to be less rare than they once were. This, however, is more likely the result of the referring of youngsters with serious or unusual diseases to a children's hospital rather than of a marked change in the character of the disease. The third member of the group, eosinophilic granuloma, is still most unusual—especially if the skin alone is affected.

Eosinophilic granuloma as it involves the bone is seen frequently enough to be suspected after the viewing of an x-ray picture of the involved site, and the diagnosis may be readily confirmed by a biopsy of the bone. The evaluation of the problem of eosinophilic granuloma is not clear-cut, however, when the skin alone is involved. A primary eosinophilic nodular infiltration of the skin may have the histopathologic features of the Letterer-Siwe or the Hand-Schüller-Christian state and yet in no way simulate the course of these diseases. Repeated biopsies may have to be performed on various skin lesions, along with a general hematological survey and x-ray studies of the long bones, procedures which may extend over a period of weeks, before one can be certain of the diagnosis.

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Despite the similarity of the tissues of the reticuloendothelioses, one has only to chart the various life spans to realize that the eosinophilic granuloma (skin and/or bone) group has but little menace to life. Confusion among observers can be clarified only by the continued reporting of such patients. The need for clarification is evident when Allen [2] contends that "eosinophilic granuloma of bone . . . has been equated with various kinds of eosinophilic granuloma of skin on apparently insufficient basis" and in the views of Woerdeman and Prakken [3] that primary eosinophilic granulomas of the skin "may appear combined with eosinophilic granuloma of bone and in a lesser degree with Hand-Schüller-Christian and Letterer-Siwe diseases."

Our patient, although she was diagnosed early in the disease process as having an example of eosinophilic granuloma of the skin, required prolonged study before the lesions disappeared and one could be sure that a severe type of normocholesteremic lipoidosis would not result.

Report of Case

A Negro girl was first seen at the age of 6 weeks. The mother stated that the child was the product of a full-term uneventful pregnancy and that she developed small growths on the skin at the age of 2 weeks. There were no other complaints, and the child's growth and development were within normal limits.

Examination of the skin showed about 20 papules dispersed over the trunk and extremities, with no evident symmetry of the lesions. Each papule was about 5 mm. in diameter, firm and with no tendency to break down (Fig. 1). The only other positive finding in the physical examination was an umbilical hernia.

A biopsy was performed on a lesion present on the child's hand, and on histopathologic examination (Fig. 2) a massive infiltrate was seen throughout the dermis. This was composed of histiocytes

Fig. 1.—Typical lesion of eosinophilic granuloma of the skin.

and a tremendous number of eosinophilic leukocytes. The histiocytes had large vesicular nuclei and a uniform cytoplasm. No evidence of lipid deposition was seen. A bone survey showed no osseous pathology. Chemical examinations of the blood, including cholesterol studies, were within normal limits. A tibial marrow study revealed a relative increase in eosinophilic myelocytes, but the findings were not diagnostic of any specific disease.

A second biopsy, performed when the patient was 3 months of age, showed that the heavy eosinophilic leukocyte infiltration was still present along with histiocytes and lymphocytes. However, repeating the tissue studies one month later showed that, while the histiocytes and lymphocytes still were present in the upper dermis, there was a marked clearing of the eosinophilic leukocytes. Foam cells were not present at any time.

The child was examined frequently in the clinic and hospital because of several recurrent severe upper respiratory tract infections, diarrhea, and pneumonia. By the age of 13 months all of the lesions on the skin had disappeared. Repeated blood cell counts during the first year of life were within the normal range, and at no time was there an eosinophilia of the peripheral blood. In addition, a repeat of the bone survey at the 13-month period showed no deviation from the normal.

Comment

It is doubtful that such a patient should be included in the reticuloendotheliosis group of the nonlipid type. The evidence for exclusion is the course of the patient's disease process. Time demonstrated the benign course, which was at variance with the possible serious prognosis one would have expected from the histopathologic appear-

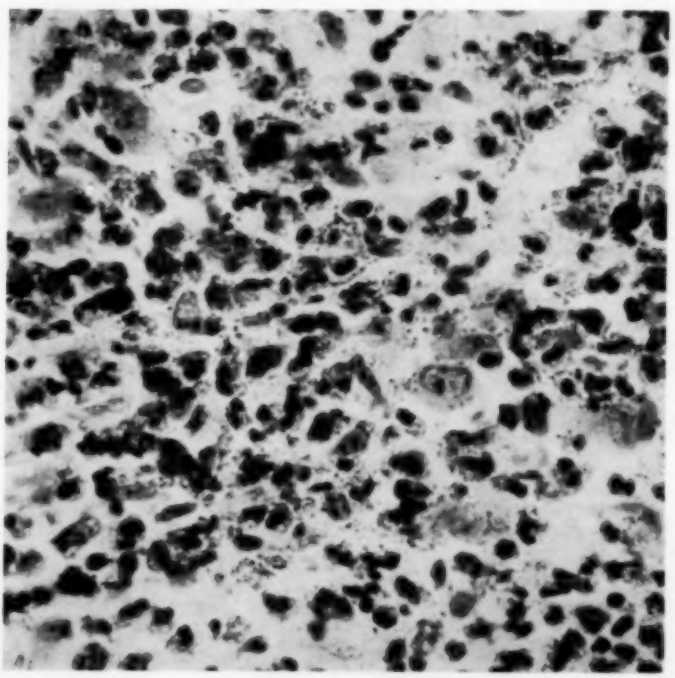

Fig. 2.—Photomicrograph (high power) of tissue from lesion shown in Figure 1. Intracellular bodies are eosinophiiic granules located within the eosinophilic leukocytes.

ance of the sections taken from the papules.

Woerdeman and Prakken in their classification of the eosinophilic granulomata suggested a grouping which they termed "reticulogranuloma eosinophilicum cutis simplex." Essentially, this consists of solitary tumors with the histopathologic features as presented in our case and a similar benign course.

Insect bites are always to be considered in a study of eosinophilic infiltrates in the skin. Allen has pointed out that one should expect to see pseudoepitheliomatous hyperplasia and spongiosis which may progress to vesiculation, along with acanthosis, parakeratosis, and hyperkeratosis. A dense dermal infiltrate is found, consisting of eosinophilic cells and histiocytes, which may simulate the group under discussion. In addition, the large numbers of plasma cells, conspicuous lymphocytic follicles with definite germinal centers, and epidermal inclusion cysts distinguish the reaction.

Summary

A patient with primary eosinophilic granulomata of the skin is reported. The purely local nature of the process and the course of the disease characterized its benign status in this case.

Although the individual lesions under the microscope may have been compatible with the findings seen in the nonlipid type of reticuloendothelioses, there were no other corroborating factors in the blood or bones. One should clearly define the type of eosinophilic granuloma under review, for the osseous type has the more serious import.

Woerdeman and Prakken's concept of "reticulogranuloma eosinophilicum cutis simplex" as a solitary lesion can safely be broadened to include patients having multiple lesions when the pathology and the course of the conditions are similar.

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Correspondence

PREMATURE AND FULL-TERM INFANTS: A COMPARISON OF THEIR MATERNAL HISTORIES

To the Editor:—I would like to comment on the interesting paper in the August issue of the A. M. A. Journal of Diseases of Children, p. 169, by Dr. Stuart S. Stevenson and his associates on the comparison of premature and full-term infants. It is commendable to see efforts to determine the cause of prematurity, since this is recognized as an obviously essential step if further progress is to be made in reducing disability through the medium of prevention. It appears unfortunate, therefore, that some of the conclusions which the authors draw from their data tend to obscure rather than clarify etiologic factors.

Since the racial differences in prematurity are so marked, it would seem essential to have comparable white and nonwhite groups before drawing conclusions about variations. One wonders, therefore, how much bias there is in the selection of the Negro mother for admission to the hospital. It is noted that the number of the nonwhite controls is only half of that of the nonwhite prematures, while there are more white controls than white prematures. One would have to assume that the 27 cards that the authors state they rejected, because they turned up as prematures, were nonwhite babies. This would seem to indicate that there was difficulty in obtaining a sufficient number of nonwhite mothers who did not give birth to premature infants. Even so, it is not completely clear that cases and controls were initially matched for race, a necessary step where racial factors are so important.

Another bit of evidence regarding bias in the selection of nonwhite patients compared to whites is the fact that there is significantly greater number of patients with "no abnormalities" among the white controls than among the nonwhite controls. This finding has been observed frequently, and it has been pointed out that when the level of abnormality in the control population is so high it is necessary to have an even larger number of cases to achieve levels of statistical significance.

This point has pertinence to the question of whether in the white race prematures are actually "the ultimate of prematurity" by being abortions. The incidence of abortions is the same in the white and nonwhite mother of premature infants. The difference between the prematures and the controls is in the same direction for both the whites and the nonwhites. It can be asked whether the failure of the difference in the nonwhite group to be statistically significant is not due merely to the fact that the level in the nonwhite controls is much higher and the total number of cases is much smaller than for the white group.

Although the authors state that they do not impute meaning unless differences are significant to the probability level of 0.05, they do not always abide by this rule in their discussion. There appear to be errors of both omission and commission in this respect. This is particularly important in relation to some of the socioeconomic indices. In this day, when there is such a high proportion of insurance coverage, it is very difficult to interpret the type of hospital accommodation in socioeconomic terms. While it is true that the control infants have a higher rate of ward admissions than the prematures, it is equally true that the premature infants have a lower rate of private accommodations than do the control infants; this difference is statistically significant when the "no cause" infants are compared with the controls. Similarly, in regard to work status there are more unskilled fathers in the premature than in the control group. Although the difference in the series is not statistically significant, this fact may be due to the relatively small numbers. Other studies with larger numbers have indicated an association between socioeconomic status and the incidence of prematurity in a white population.

It would seem unfortunate that racial and socioeconomic differences in relation to prematurity are being minimized. This is particularly true because there has been shown to be an association between the incidence of various complications of pregnancy, for instance toxemia, and the socioeconomic status of the patient. Since there might very well be a fruitful approach to the question of prevention in relation to these conditions, it would seem important to be aware of socioeconomic differences in the identification and management of patients with complications.

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To the Editor:—Thank you for letting me see Dr. Knobloch's letter concerning our article, "Premature and Full-Term Infants." I should like to comment upon some of the points which she raises.

"Comparable" white and nonwhite groups, comparable in education, socioeconomic status, etc.—that is, comparable in everything but race—would be most difficult to find, and they would be essential only if white and nonwhite groups were to be compared with each other. In our article, with the exception noted below, white study has been compared with white control and nonwhite study with nonwhite control.

Bias in the selection of the Negro mother for admission to the hospital, especially bias in regard to prematurity, the entity which is being studied, does not seem likely. The nonwhite prematurity rate (including stillbirths) was 14.0%, which approximates the rates in other series.

Cases and controls were not initially matched for race, nor does such matching seem a "necessary step" when white study is compared with white control and nonwhite study with nonwhite control. The control infants were selected merely by birth date. When it is recalled that 19.4% of the total of 4602 births were Negro, one would expect approximately 65 Negro babies to turn up among the 338 controls; actually, the number was 62. This in no way implies that the 27 control cards, rejected because they turned up as premature births, all represented Negroes; nor does it imply that there was any difficulty in finding nonwhite control mothers.

It is true that there is a significantly higher percentage of patients with "no abnormalities" among the white controls than among the nonwhite controls, but I fail to see why this is "another bit of evidence regarding bias. . . ."

Dr. Knobloch's criticism of Section O (which suggested that the problem of prematurity in the white race is obscured because the ultimate in prematurity is classified as abortion) is justified. We erred here in comparing white with nonwhite. Furthermore, in view of the high incidence of abortion in both the nonwhite study and control groups, it would probably have been more appropriate to observe, as we did in regard to syphilis, that abortion is an important problem for both groups of Negro mothers.

Dr. Knobloch comments on errors of "commission" and "omission" in abiding by our rule that a difference between two percentages will not be considered as probably meaningful unless it is greater than two times its standard error. In checking our arithmetic, I have found one error of "commission": In Section B, the incidence of "no abnormalities" among all Negro premature infants and among Negro premature stillbirths and neonatal deaths is not significantly different. Therefore, part of the concluding sentence of this Section ("The listed factors thus appear to be more frequently associated in this series . . . with those who died.") is not statistically justified in respect to Negro babies.

An error of "omission" concerns white hospital accommodations (Table 10). It is true that "no cause" premature infants have a statistically significant lower rate of private accommodations than do the controls, and we did not comment on this fact. On the other hand, it is also true that 66.1% of the study group had semiprivate accommodations as compared with 45.3% of the control group and that only 13.1% of the study group had ward accommodations as compared with 27.2% of the control group. Because the data seemed completely inconclusive, we stated that there was nothing in Table 10 to suggest that white prematurity is a socioeconomic problem in this series.

Similarly, Table 11 (white fathers' work status) offers nothing to suggest such a problem in this series. There is a higher percentage of unskilled fathers in the study than in the control group, but there is also a higher percentage of professional fathers in the study than in the control group. None of these differences, however, is significant here. We are, of course, well aware that other studies have indicated an association between socioeconomic status and white prematurity. We have attempted merely to report on what we found significant in this series, and we could find nothing in Tables 10 and 11 to support such an association.

We have not minimized racial and socioeconomic differences in relation to prematurity. We have analyzed data which concern the experience of one lying-in hospital and have thought it worth while to publish this analysis. If some of our conclusions differ from those of other authors, it may be because numbers are small. It may also be because the problems which are associated with prematurity in this community are different.

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Abstracts from Current Literature

American Heart Journal, St. Louis

53, No. 6 (June) 1957

The Electrocardiogram in Tetanus. Mario R. García-Palmieri, M.D., and Ricardo Ramírez.—p. 809.
Frequency of Rheumatic Heart Disease in Miami, Florida: Autopsy Findings. Milton S. Saslaw and Lawson C. Johnson.—p. 814.
* The Respiratory Complications of Congenital Heart Disease. George M. Maxwell.—p. 829.
Studies in Angiocardiography: The Problems Involved in the Rapid, Selective, and Safe Injections of Radiopaque Materials; Development of a Special Catheter for Selective Angiocardiography, Antonio Rodríguez-Alvarez and Gloria Martínez de Rodríguez.—p. 841.

54, No. 1 (July) 1957

Transposition of the Aorta and Pulmonary Artery with Pulmonary Stenosis. W. P. Cleland, J. F. Goodwin, R. E. Steiner, and M. Zoob.—p. 10.
Congenital Deaf-Mutism, Functional Heart Disease with Prolongation of the Q-T Interval, and Sudden Death. Anton Jervell and Fred Lange-Nielsen.—p. 59.
* Fatal Myocarditis Following Smallpox Vaccination. Jorgen B. Dalgaard.—p. 156.

The Respiratory Complications of Congenital Heart Disease.—The author presents the incidence of all types of respiratory complications, other than simple coryza, in a series of 173 consecutive cases of congenital heart disease. Respiratory infections occurred in 33% to 69% of the cases, with about equal magnitude in those with increased and those with decreased pulmonary blood flow. Only in uncomplicated coarctation of the adult type and in pure pulmonary stenosis was the incidence of respiratory infections found to be low. The author therefore postulates that it is the alteration in pulmonary blood flow, either pulmonary plethora or pulmonary oligemia, which leads to increased respiratory infections.

In many of these patients respiratory infections occurred with remarkable frequency and constituted the leading complaint in a high percentage of cases, the parents being more impressed by the recurrent respiratory illnesses than by the cardiac disability per se. This was equally true in tetralogy of Fallot and atrial septal defect.

The infections usually had their onset when the patient was 3 to 4 months of age, in both the cyanotic and acynotic types of congenital heart disease, and occurred with undiminished frequency for the first two to three years of life. Thereafter there was a slow decline in frequency. The span of years through which these patients can be followed is limited. Many undergo surgery. Many die. Respiratory infections may, of course, be the precipitating cause of death.

For prevention of these infections, prophylactic use of penicillin may prove beneficial. While use of penicillin in these cases lacks the specificity of streptococcal prophylaxis as used in rheumatic fever, and while statistical evidence of its value is not available and would be extremely difficult to accumulate, penicillin prophylaxis may be worthy of trial in selected cases.

Fatal Myocarditis Following Smallpox Vaccination.—A case report is presented of a 22-year-old conscript, previously in good health, who was vaccinated in the course of routine mass vaccination. He had undergone previous vaccination as a child without complications. The revaccination resulted in a primary take. On the eighth day, the patient was admitted to the infirmary with headache, fever, tachycardia, and palor. There was a pronounced local reaction with regional axillary lymphadenitis at the vaccination site. Otherwise the physical examination was not remarkable. No electrocardiogram was taken. The following morning the patient uttered a loud cry and became unconscious. A very rapid pulse was noted. Death ensued within five minutes.

At autopsy, in addition to the vaccination wounds, there was 40 cc. of serous exudate in the pericardial sack. The heart was of normal size, and no abnormalities were noted in the endocardium, valves, or coronary arteries. The myocardium, especially of the left ventricle, was flabby, with pale and hyperemic areas interchanging. The lungs were congested, and the

spleen was about double the normal size. The leptomeninges were hyperemic, but the brain appeared normal.

Histologic examination revealed, particularly in the left ventricular myocardium, numerous foci of acute degeneration and pronounced infiltration with granulocytes and some lymphocytes. Between these areas normal myofibrils were found. There was no evidence of encephalitis, and the meninges revealed no signs of inflammation.

A bacteriologic examination was not performed, but in the absence of any known infectious disease it was concluded that the acute fatal myocarditis was a smallpox vaccination sequela. One other very similar case in which death occurred nine days after vaccination has been reported, and there are two additional cases reported of electrocardiographic and clinical evidence of nonfatal postvaccination myocarditis.

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

76 (Oct.) 1956

* Congenital Mitral Stenosis: Roentgen Study of Its Manifestations. Theodore F. Hilbish and Robert N. Cooley.—p. 743.
* Bilateral Ductus Arteriosus with Right Aortic Arch and Right-Sided Descending Aorta: Report of Case. Edward H. Bergman and Jesse E. Edwards.—p. 758.

77 (Jan.) 1957

* Water Intoxication: Report of Fatality Following a Barium Enema. Carrell A. Paterson and Glen G. Cayler.—p. 69.

Congenital Mitral Stenosis: Roentgen Study of Its Manifestations.—This is a rare congenital anomaly and as an accompaniment of some other malformation is uncommon. There is disagreement as to whether this represents a congenital anomaly or represents a fetal endocarditis. Farber and Hubbard believe that both types occur. As in the acquired type, some degree of insufficiency accompanies many of the cases of congenital mitral stenosis, and the hemodynamic effects are not different.

The natural course of the uncomplicated case depends on the severity of the stenosis. However, when associated with another anomaly the disability due to the combined defects may be early in onset and severe. When accompanying coarctation of the aorta it may account for early heart failure and make surgical correction more hazardous. When associated with a patent ductus arteriosus a distinctive clinical syndrome may be noted, the chief feature of which is an uneven distribution of cyanosis between the upper and lower portions of the body.

Two cases were proven at autopsy and fifteen cases were diagnosed on presumptive evidence.

The following conditions are briefly discussed: Group I, congenital mitral stenosis with a reverse flow through a patent ductus arteriosus, three cases; Group II, congenital mitral stenosis with a patent ductus arteriosus without a reverse flow, three cases; Group III, congenital mitral stenosis associated with coarctation of the aorta, six cases; Group IV, mitral stenosis with an intraventricular septal defect, two cases; Group V, uncomplicated mitral stenosis, three cases.

In each of these cases in which angiocardiography was done stagnation of blood was found in the left atrium, and enlargement of the left atrium was seen in all but one case.

Bilateral Ductus Arteriosus with Right Aortic Arch and Right-Sided Descending Aorta: Report of Case.—In other cases reported the bilateral ductus arteriosus is associated with absence of the proximal portion of a pulmonary artery and commonly with other serious intercardiac defects. This was not so in this case.

This case is that of a boy who died at 6 days of age. At autopsy the aorta arose from the left ventricle in a normal manner. The aortic arch and descending aorta were on the right. There was a bilateral ductus arteriosus, and the left subclavian arose from the left ductus arteriosus.

Water Intoxication: Report of Fatality Following a Barium Enema.—This is a single case report of a 3-year-old boy who died of water intoxication following a barium enema. Previous reports have occurred in the literature reporting death due to water intoxication, hypervolemia and hypoelectrolymia, as direct result of hypotonic enemas in children with megacolon. This is the first known report of such an occurrence in a normal child.

This child had had a poor intake of fluids on the day preceding the study and after the barium enema he was given a tap water enema, the combination of which seemed to precipitate the fatal electrolyte disturbance.

American Review of Tuberculosis and Pulmonary Diseases, New York

75, No. 6 (June) 1957

Pulmonary Tuberculosis Developing in Persons Observed from Childhood. Brian C. Thompson.—p. 885.
* Skeletal Tuberculosis in Children Treated for Primary and Miliary Tuberculosis. Lillian Milgram.—p. 897.
Demonstration of Circulating Antibodies to M. Tuberculosis in Humans: I. Technique. Slater M. Dozier, Matthew H. Fusillo, and George E. Woodham.—p. 949.
Demonstration of Circulating Antibodies to M. Tuberculosis in Humans: II. Clinical Laboratory Studies. Matthew H. Fusillo, Daniel L. Weiss, and Slater M. Dozier.—p. 954.
Formation of Bullae or Cystlike Cavities During Chemotherapy in Rabbits with Pulmonary Tuberculosis. William Steenken Jr. and Emanuel Wolinsky.—p. 965.
Remarks on the Epidemiology of Tuberculosis: A Review. C. Eugene Woodruff.—p. 975.
Trials with Tuberculosis Vaccine, Irradiated. Armando Pareja Coronel.—p. 987.
Reliability of a Microbiologic Assay Technique for Measuring Low Concentrations of Isoniazid. J. C. Bell and D. K. Riemensnider.—p. 992.
Use of a Serum Microbiologic Assay Technique for Estimating Patterns of Isoniazid Metabolism. J. C. Bell and D. K. Riemensnider.—p. 995.
Serum Paper Electrophoretic Patterns of Tuberculous Patients Presenting Therapeutic Problems. J. H. Maher et al.—p. 999.
A Rapid Microculture Method for the Isolation of Tubercle Bacilli. A. Hambleton and J. Ozols.—p. 1007.
Statement on Pyrazinamide. Statement by the Committee on Therapy.—p. 1012.
Statement on Cycloserine. Statement by the Committee on Therapy.—p. 1016.

Skeletal Tuberculosis in Children Treated for Primary and Miliary Tuberculosis.—A group of children less than 13 years of age, with roentgenographic evidence of primary tuberculosis, was followed for two to eight years. The children were divided into three groups: (1) patients with primary tuberculosis, in which the incidence of bone lesions in those treated with streptomycin or isoniazid was compared with that in untreated patients; (2) those with miliary tuberculosis, complicating primary tuberculosis, treated with a sulfone alone, and (3) an additional group of patients with primary tuberculosis, also untreated.

During the follow-up period, skeletal lesions occurred with greater frequency among the survivors of miliary tuberculosis. The incidence was low among children treated for indications other than miliary disease, including those treated for skeletal tuberculosis, and was lower than in the untreated group. The author feels that chemotherapy given to children with early primary infection can, to a greater or less extent, prevent tuberculosis of the bone.

Suggestion is made that the bones are infected early in the course of primary tuberculosis and that chemotherapy acts on already established foci. Since there is evidence that there is widespread involvement of the bone marrow when treatment of miliary tuberculosis is begun, it may be concluded that such foci probably account for the frequency of clinical bone tuberculosis in treated generalized tuberculosis.

Annals of Internal Medicine, Lancaster, Pa.

45:331-560 (Sept.) 1956

The Present Status of Etiologic Discovery in Viral Diseases. John F. Enders.—p. 331.
* The Importance of the Fractional Serum Bilirubin Determination in Clinical Medicine. C. J. Watson.—p. 351.
Pseudomembranous Enterocolitis and Antibiotics. C. R. Newman.—p. 409.
Constrictive Pericarditis: A Review and Long-Term Follow-Up of 78 Cases. John C. Dalton, R. J. Pearson Jr., and Paul D. White.—p. 445.
Infiltrative Eosinophilia. R. S. Díaz-Rivera, F. Ramos-Morales, M. R. García-Palmieri, Z. R. Sotomayor, and A. A. Cintrón-Rivera.—p. 459.
Varicella Pneumonia. Ray G. Cowley, William E. Crew, and Gerard R. Hassett.—p. 518.
Congenital Aneurysm of the Noncoronary Sinus of Valsalva Leading to Complete Heart Block. Edmon B. Lee, Oscar J. Krieger, and Norman K. Lee.—p. 525.

45:561-736 (Oct.) 1956

Fructosuria. Alfred R. Lenzner.—p. 702.
The Rh-Hr Types: A Complex Problem in Serology, Genetics and Nomenclature. A. S. Wiener and I. B. Wexler.—p. 725.

45, No. 5 (Nov.) 1956

Congenital Indifference to Pain. Macdonald Critchley.—p. 757.
* The Current Problem of Staphylococcal Infections. David E. Rogers.—p. 748.
The Diagnostic, Prognostic, and Epidemiologic Significance of Serum Glutamic Oxaloacetic Transaminase (SCO-T): Alterations in Acute Hepatitis. Felix Wroblewski, George Jervis, and John S. LaDue.—p. 782.
Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Eleventh Rheumatism Review). William D. Robinson, Joseph J. Bunim, William S. Clark, Darrell C. Crain, Ephraim P. Engleman, Donald C. Graham, Max. M. Montgomery, Bernard M. Norcross, Charles Ragan, Marian W. Ropes, Edward F. Rosenberg, and Charley J. Smyth.—p. 831.

46, No. 1 (Jan.) 1957

Problems in the Management of Ulcerative Colitis, with Particular Reference to ACTH and the Adrenal Steroids. Manuel Sklar, Joseph B. Kirsner, and Walter L. Palmer.—p. 1.
Bezoars. Arvel E. Haley.—p. 30.
Polycythemia of Obesity: Further Studies of Its Mechanism and a Report of Two Additional Cases. Max H. Weil and Ananda S. Prasad.—p. 60.
Amino-Aciduria with Cystinosis: Case Report with Determination of Urinary Amino Acids and Ocular Cystine. Philip L. Dern.—p. 138.
Goiters in Twins Resulting from Propylthiouracil Given During Pregnancy. LeRoy K. Branch and Sanford W. Tuthill.—p. 145.

The Importance of the Fractional Serum Bilirubin Determination in Clinical Medicine. Van den Bergh, who first applied the diazo reaction for the determination of bilirubin, recognized that it proceeded in two phases, a prompt direct reaction requiring seconds and an indirect reaction beginning in two to four minutes and greatly accelerated by the addition of alcohol. Subsequent studies of time reaction curves have shown that the main period of transition occurs at about one minute; therefore, measurement of the direct value should be made at this time. Direct-reacting bilirubin is water-soluble, or polar, while indirect-reacting bilirubin is chloroform-soluble, or nonpolar. Recently, it has been shown that indirect-reacting bilirubin is indistinguishable from chemically pure, free crystalline bilirubin. The older concept that indirect-reacting bilirubin is a complex with the protein globin now seems unlikely. On the other hand, direct-reacting bilirubin has been shown to be a complex of bilirubin and an anion, probably glucuronic acid.

Based on an analysis of 889 serum bilirubin determinations in 702 patients with one-minute values greater than 0.29 per 100 cc. or total bilirubin greater than 1.5 mg. per 100 cc., the fractional determination has been useful in three respects. First, elevation of the one-minute fraction with normal indirect fraction occurs in preicteric or anicteric hepatitis, common duct stone without jaundice, hepatic carcinomatosis, and cases of cirrhosis with cholangiolitic features. In all of these situations the one-minute bilirubin is abnormal where the total bilirubin determination fails to reveal the presence of disease. Second, elevation of the indirect fraction with little or no increase in the direct fraction occurs in retention jaundice, which is due to hemolysis or impaired hepatocellular function. Certain cases of cardiac jaundice, some of subsiding infectious hepatitis, and the Gilbert type of constitutional hepatic dysfunction belong in this category. Third, in regurgitation jaundice both fractions are usually increased. Often this determination fails to distinguish between parenchymal and extrahepatic causes, but when the total bilirubin is elevated (>1.5) and the one-minute value is less than 40% of the total, extrahepatic obstruction may be considered very unlikely. Most cases of hepatitis and biliary tract cancer have ratios greater than 50%. Low ratios occurring in hepatitis or cirrhosis suggest the presence of hemolytic complications.

The Current Problem of Staphylococcal Infections.—Staphylococcal infections have proved more difficult than others to treat with antibiotics because of certain peculiar factors in the parasite-host biologic relationship. On the side of the organism, virulence is enhanced by the ability to produce a toxin causing dermal necrosis, by the ability to survive after phagocytosis, and by the formation of an isolated milieu in abscesses, where staphylococcal growth is favored, the action of antibiotics is impaired, and the formation of antibodies is prevented. Above all, the appearance of antibiotic-resistant mutant strains has quickly followed the introduction of each new therapeutic agent. At present about 80% of strains isolated from hospitalized patients but only 20% of strains isolated from outpatients are resistant to penicillin, and the same tendancy has been noted with streptomycin and the tetracyclines. Resistance can even develop in the asymptomatic carrier state in persons receiving prophylactic antibiotic treatment. Certain host factors which favor staphylococcal

infections are diabetes, poor nutrition, filth, exposure of the skin to irritants, excessive sebaceous gland activity, foreign bodies, stress, and influenza (which always precedes staphylococcal pneumonia in adults).

Although staphylococcal septicemia in pediatric patients has decreased sharply at the New York Hospital since 1940, the incidence and mortality from staphylococcal pneumonia in adults have greatly increased. Also, whereas the patient typically affected used to be an otherwise healthy person admitted specifically for staphylococcal pneumonia, nowadays this disease mainly attacks patients already in the hospital with some advanced disease. The Staphylococcus is replacing the Pneumococcus as a threat to debilitated patients.

The treatment of choice is still aqueous penicillin in doses of 6,000,000 to 12,000,000 units daily, usually in combination with streptomycin. When the strain is resistant to these drugs in vitro, they may still be successful, especially if even higher doses of penicillin are used. Most strains are not yet resistant to erythromycin, chloramphenicol, or bacitracin, and so some effective antibiotic regimen can usually be found. More attention should be given to other measures, such as surgical drainage, treatment of the underlying disease if possible, and prevention. The indiscriminate use of antibiotics in patients without infection should be stopped, whereas potent antistaphylococcal drugs should be used in those who are known to be in specific danger of such infections. Sources of staphylococci should be isolated; proper hospital techniques should be employed to prevent cross infection, and appropriate treatment should be given.

Future advances will come from more complete knowledge of the host-parasite biology and the development of therapeutic measures which tip the balance against the Staphylococcus.

Blood, New York

12, No. 3 (March) 1957

Combinations of Hemoglobin G, Hemoglobin S and Thalassemia Occurring in One Family. W. W. Zuelzer, J. V. Neel, A. R. Robinson, and S. F. Kaufman.—p. 238.
The Bone Marrow in Pregnancy and the Puerperium. Louis Lowenstein and Catherina A. Bramlage.—p. 261.
* Panels in Therapy: XIII. Hypoplastic Anemia of Childhood. Wolf W. Zuelzer, Carl H. Smith, and Philip Sturgeon.—p. 303.

12, No. 4 (April) 1957

Bone Marrow Transplantation—A Present-Day Challenge. William Dameshek.—p. 321.
* The Submicroscopic Morphology of Gaucher Cells. Quin B. DeMarsh and Jean Kautz.—p. 324.
The Pseudo-L. E. Cell Phenomenon, with Report of a Case. N. B. Kurnick.—p. 382.

12, No. 5 (May) 1957

* Microdrepanocytic Disease in Greece. C. Choremis and L. Zannos.—p. 454.
A Case of Congenital Afibrinogenemia. P. B. Fernando and B. D. Dharmasena.—p. 474.

Panels in Therapy: XIII. Hypoplastic Anemia of Childhood.—The panelists discuss the problem of therapy of a child of 3 with chronic normochromic normocytic anemia with a normally cellular marrow except for greatly reduced numbers of normoblasts. Dr. Wolf Zuelzer points out that such a picture could be produced by a number of etiologic possibilities: chronic infection, renal disease, malignancy, an unusual leukemia or acquired or congenital hypoplastic anemia. Treatment would depend on the fundamental cause of the difficulty.

Dr. Carl Smith and Dr. Philip Sturgeon regard pure red-cell or chronic aregenerative anemia as the most likely diagnosis in the instance cited and present an outline of therapy for this disorder. They agree that after a period of observation a course of steroid therapy would be tried for about 6 to 12 weeks. Supportive therapy with packed red cell transfusions is recommended to maintain the hemoglobin above 6 to 7 gm. Splenectomy, it is agreed, might be tried if all else fails to ameliorate the situation.

Skillful application of these three measures may serve in some to bring dramatic response or in others to tide the patient over until the time of a spontaneous remission.

A variety of other agents have been tried, including cobalt, diathermy of the marrow, vitamin B, etc., but their variety and number indicate that we have no good single therapeutic agent, and understanding of the basic process that leads to lack of red cell precursors will have to be elucidated if we are to improve the therapy of hypoplastic anemia in childhood.

The Submicroscopic Morphology of Gaucher Cells.—Investigation of the characteristic large cells found in the bone marrow and spleen in Gaucher's disease was made with use of electron microscopy as well as phase-contrast and polarizing microscopy. Submicroscopic tubular structures within dense elongate or crescent-shaped bodies are described. It is suggested that these structures represent molecular kerasin or lipoprotein units known from biochemical and histochemical evidence to be present in Gaucher cells. Numerous microvesicles were found near the complex cell border, suggesting transport of some substance across an active cell membrane. The literature concerning some aspects of Gaucher's disease is summarized, and an attempt is made to correlate the morphologic findings with clinical and biochemical information concerning Gaucher's disease.

It is postulated that the fibrils are an abnormal constituent of the marrow cells, representing a lipoprotein complex. If the lipoprotein is synthesized outside the cells, it, or an immediate precursor, may be actively transported across the cell membrane in the microvesicles noted near the cell border.

Microdrepanocytic Disease in Greece.—Microdrepanocytic disease, or thalassemia-hemoglobin S disease, is the product of an interaction between two nonallelomorphic genes, i. e., the sickle gene and the thalassemia gene. Patients with microdrepanocytic disease may inherit one abnormal gene from each parent or both abnormal genes from one parent. A study was made in Greece to determine the comparative incidence of microdrepanocytic disease and sickle-cell disease. Study of the parents' hemoglobin pattern and red cell morphology was necessary in order that a differential diagnosis could be made between sickle-cell disease and thalassemia-hemoglobin S disease in the patients.

Among 57 patients with clinical and hematological picture of sickle-cell anemia, it was found after examination of the parents of these patients that 44 could be defined as having microdrepanocytic disease and 13 as having sickle-cell anemia, as expected, since thalassemia trait is more frequent in Greece than is sickle trait.

Geographic distribution of microdrepanocytic disease was found to be much wider than that of sickle-cell disease, which occurs in areas where the trait has been found in high frequency.

Canadian Medical Association Journal, Montreal

76 (May 15) 1957

Summer Diarrhoea. J. H. Ebbs.—p. 869.

76 (June 15) 1957

* Notes on Neonatal Thrush and Its Epidemiology. Antony Shardt and T. E. Roy.—p. 1029.

Solitary Eosinophilic Granuloma of Skull (1950); Osteochondritis Dissecans of Knee (1954). George McClelland Bastedo.—p. 1054.

77 (July 1) 1957

* Outbreak of Aseptic Meningitis (Meningoencephalitis) with Rubelliform Rash: Toronto, 1956. R. A. Laforest, G. A. McNaughton, A. J. Beale, Mairin Clarke, Norma Davis, I. Sultanian, and A. J. Rhodes.—p. 1.

Severe Hemolytic Disease of the Newborn Due Probably to the Combined Action of Anti-A and Anti-S. B. Chown, Marion Lewis, and B. Best.—p. 31.

Spontaneous Rupture of the Spleen in an Erythroblastotic Infant. D. J. Murray, P. W. Davey, and G. M. Martin.—p. 37.

77 (July 15) 1957

* Haemolytic Disease of the Newborn Due to ABO Isoimmunization. Morris Sabin and Louis Lowenstein.—p. 92.

1000 Cases of Tonsillectomy in a Prepayment Plan: Preoperative and Postoperative History. H. leRiche and W. B. Stiver.—p. 109.

77 (Aug. 1) 1957

* Malaria in a Saskatchewan-Born Infant. H. Crossley.—p. 225.

* A Normal Child Following Insulin Coma Therapy in Early Pregnancy. B. A. Boyd.—p. 227.

Notes on Neonatal Thrush and Its Epidemiology.—Candida albicans in the vaginal flora of the parturient mother is an important factor in the development of thrush in the

newborn infant. In a series of 128 infants, 9 developed thrush. Two cases were probably related to cross infection, but the remaining seven babies acquired the infection primarily from their mothers. The mothers, then, are the main potential sources of danger, and antepartum vaginal cultures might well be taken from all women during pregnancy. As a prophylactic measure nystatin appears most suitable for use in both mother and infant.

Outbreak of Aseptic Meningitis (Meningoencephalitis) with Rubelliform Rash: Toronto, 1956.—The authors describe an outbreak of aseptic meningitis in Toronto characterized by the appearance of a maculopapular rubelliform rash. The authors observed 115 children, and the rubelliform rash appeared in 50, or 43%. The main symptoms were fever, stiff neck, headache, and vomiting. The spinal fluid cell counts tended to be high, the mean cell count being 694 cells per cubic millimeter. This is considerably higher than that found in poliomyelitis or Coxsackie meningitis. The convalescence was uneventful. The average duration of stay in hospital was six days, and when the patients were examined some six weeks after discharge there was no evidence of paralysis in any patient.

Specimens of stool, cerebrospinal fluid, and blood were studied, and from 94 stool preparations 58 viruses were recovered. From the 48 samples of cerebrospinal fluid used 15 viruses were isolated. All these viruses produced the cytopathogenic changes in tissue cultures. None of these agents was neutralized by pooled antisera to poliomyelitis viruses Types 1, 2, and 3. The details of further virological studies are given. The laboratory findings suggest that the etiologic agent was a virus related to ECHO virus Type 9.

Hemolytic Disease of the Newborn Due to ABC Isoimmunization.—Seventeen cases of hemolytic disease due to ABO incompatibility were observed at the Royal Victoria Hospital in five years. It is usually a mild disease, and the most useful criteria for diagnosis are a history of jaundice within the first 24 hours after birth and a Group O mother with a Group A (or B) baby. Exchange transfusion was administered in nine cases, and the indications for the transfusion are discussed. These are much the same as in Rh incompatibility. There were no deaths and no kernicterus. The incidence of ABO incompatibility was low, 17 cases in 16,621 deliveries.

Malaria in a Saskatchewan-Born Infant.—An illness in an 11-month-old Chinese girl whose parents were both from the Canton Province in China was diagnosed as malaria. Two months previously the baby had been given 3 cc. of the mother's blood intramuscularly. Both the mother and the father had previously had malaria, and it is presumed that the baby obtained the malaria from this one injection of her mother's blood.

A Normal Child Following Insulin Coma Therapy in Early Pregnancy.—The author notes that a review of the literature indicates that some deformity, abortion, or stillbirth is to be expected if insulin coma precedes the 10th week of pregnancy. This form of treatment therefore is not customarily given to women known to be pregnant.

The case described is that of a pregnant woman who received insulin coma therapy with 32 treatments involving 10 half-hour comas in the first 11 weeks of pregnancy. The child, now 3½ years old, shows no apparent damage from this experience, and the history and observations indicated a normal rate of physical and mental development.

Circulation, New York

15, No. 3 (March) 1957

* Isolated Congenital Mitral Stenosis: Report of Two Cases with Mitral Valvotomy in One. J. L. Braudo, S. N. Javett, D. I. Adler, and I. Kessel.—p. 358.

Congenital Absence of the Pulmonary Valve. Luvien A. Campeau, Paul E. Ruble, and Warren B. Cooksey.—p. 397.

15, No. 4 (April) 1957

Bacterial Endocarditis Following Cardiac Surgery. Clarence Denton, Elias G. Pappas, Joseph F. Uricchio, Harry Goldberg, and William Likoff.—p. 525.

Interatrial-Pressure Relationships After Closure of Atrial Septal Defects in Man. Albert H. Pemberton, John W. Kirklin, and Earl H. Wood.—p. 568.

American Heart Association: Congenital Cardiac Defects; A Physician's Guide for Evaluation and Management. Ruth Whittemore, S. Gilbert Blount Jr., Sidney Blumenthal, Frank Gleen, Edward C. Lambert, and Helen B. Taussig.—p. 631.

15, No. 5 (May) 1957

Cor Triloculare Biotriatum. Donald Heath.—p. 701.
Cardiovascular Disturbances in Poliomyelitis. Louis Weinstein.—p. 735.

15, No. 6 (June) 1957

Valvular Pulmonary Stenosis with Intact Ventricular System: Clinical and Physiologic Response to Open Valvuloplasty. S. G. Blount, J. von Elk, O. J. Balchum, and Henry Swan.—p. 814.
Stenosis of a Branch of the Pulmonary Artery: An Additional Cause of Continuous Murmurs over the Chest. F. Eldridge, A. Selzer, and H. Hultgren.—p. 865.
Selection of Patients for Mitral and Aortic Valvuloplasty. Q. B. Ellis, W. H. Abelmann, and D. E. Harken.—p. 924.

15, No. 7 (July) 1957

Tricuspid Stenosis: Physiologic Criteria for Diagnosis and Hemodynamic Abnormalities. T. Killip III and D. Qukos.—p. 3.
Anomalous Connection of Right Pulmonary Veins to Superior Vena Cava with Arterotrial Communications: Hemodynamic Data in Eight Cases. H. J. C. Swan, J. W. Kirklin, Q. Becur, and E. H. Wood.—p. 54.

Isolated Congenital Mitral Stenosis: Report of Two Cases with Mitral Valvotomy in One.—The authors report two cases of isolated congenital mitral stenosis in two young infants. The diagnosis in one was proved at autopsy. The other was diagnosed clinically; this patient is still living and moderately well 16 months after mitral valvotomy. The essential features of all the cases of isolated congenital mitral stenosis previously reported in the literature supplemented with their two cases are studied. The authors described symptoms as usually beginning at birth, but with possible delay until 2 years of age. Growth failure and dyspnea were common in most cases. The most frequent physical findings were congestive failure, cardiomegaly, apical systolic murmur, and accentuated pulmonic second sound. Periodic episodes of cyanosis did occur but were not persistent. Chest plates revealed cardiac enlargement, pulmonary plethora, and left and usually right atrial enlargement together with right ventricular hypertrophy. Angiocardiography was diagnostic, since the dilated left atrium retained the dye for an abnormally long time because of the stenosed mitral valve. The pathologic changes in the mitral valve were described.

Minerva pediatrica, Turin

9 (April 7) 1957

* Transaminase Activity in the Serum of Children with Certain Infectious Diseases. P. Tolentino and M. Rossi.—p. 377.
The Duodenal Enzymes in Kwashiorkor (Sicilian) and in Some Dystrophic Conditions in Infants. G. Russo and P. Battitta.—p. 382.
Pulmonary Pathology in Infants, Caused by Staphylococci. A. Benevolo.—p. 395.

9, Nos. 19 and 20 (May 19) 1957

*Congenital Cardiovascular Pathology
Clinical Diagnosis. M. Gomirato Sandrucci.—p. 539.
Electrocardiography in Diagnosis. G. Boni.—p. 553.
Phonography in Diagnosis. G. Boni.—p. 562.
Changes in Somatic and Mental Development. M. Malaspins.—p. 567.
Pre- and Postoperative Medical Therapy. E. Segagni.—p. 576.
Prognosis. G. Guassardo.—p. 588.

9 (June 2) 1957

* Cases of Illness Due to the Coxsackie Virus. M. Crisalli and S. Scarabicchi.—p. 593.
Variations in the Perchloric-Soluble Mucoprotein Content of the Serum and in the Diphenylamine Reaction of the Serum in Children with Rheumatic Fever. P. N. de Sario and F. Piccotti.—p. 605.
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The Protein, Mucoprotein and Polyccharide Contents in the Serum of the Umbilical Cord. P. B. de Sario.—p. 611.
* The Serum Protein Picture in Children with Tuberculosis, as Determined by Electrophoresis. E. Sacconaghi and E. Fumagalli.—p. 613.

9 (June 16) 1957

* Oxalosis, a New Metabolic Disease of the Storage Type. G. de Toni, P. Durand, and C. Rosso.—p. 623.
* A Case of Methemoglobinemia Due to Aniline. P. C. Gamalero.—p. 638.
* Some Anatomical Abnormalities of the Gastrointestinal Tract with Vomiting and Malnutrition in Infants. G. Torricelli and G. Bizzi.—p. 647.

Transaminase Activity in the Serum of Children with Certain Infectious Diseases. Transaminase is an enzyme which leads to the exchange of an amino group (NH_2) from an α-amino acid with a keto group (CO) of an α-keto acid.

In the present study, the method of Tonhazy, White, and Umbreit was used. The patient's serum was exposed to an excess of aspartate and α-ketoglutarate at 37 C for 10 minutes. The enzyme activity is evaluated by the amount of pyruvate formed, as determined colorimetrically.

The transaminase activity was measured in the sera of children, both normal and with various infectious diseases, including scarlet fever, chickenpox, mumps, mononucleosis, pertussis, measles, poliomyelitis, infectious arthritis, and hepatitis. Only in the cases of infectious hepatitis was the transaminase activity above normal; in these cases it was 10 to 20 times normal.

The suggested value of this test is in the early recognition of acute or relapsing cases and in the diagnosis of cases of hepatitis without jaundice.

Congenital Cardiovascular Pathology.—These entire numbers of *Minerva pediatrica* are devoted to various aspects of congenital heart disease, most of the clinical observations and data being based on 444 cases seen at the pediatric clinic of the University of Turin.

History, inspection, palpation, percussion, and auscultation should yield an exact diagnosis of the type of cardiac lesion in 37% of the cyanotic patients and in 60% of the noncyanotic ones. The age at which cyanosis appeared, the frequency and timing of collateral signs and symptoms, and the location, intensity, and nature of murmurs are statistically recorded for the various types of heart lesions among these patients.

Electrocardiography is of positive diagnostic value only in the diagnosis of dextrocardia, abnormalities of the origin of the left coronary artery, and tricuspid atresia. It will also give information as to right- or left-sided hypertrophy of the heart. It offers interesting information as to the changes and benefits which result from cardiac surgery.

The cyanotic child with congenital heart disease tends to be underweight and of normal height for age; the noncyanotic child tends to be overweight in 63% of the cases and overheight for age in 70%. Mental retardation was found only in some of the cyanotic cases. The postoperative patients have shown favorable responses in both their somatic and their social development.

One hundred five patients with the tetralogy of Fallot have been operated upon; evaluation of their condition some time later showed excellent or good results in 76% and unchanged or poor results in 10%. Valvulotomy in cases of trilogy of Fallot showed excellent or good results in 91% and poor results in only 4% of the cases. Satisfactory postoperative improvement resulted in 91% of the patients with pure stenosis of the pulmonary artery.

Cases of Illness Due to the Coxsackie Virus.—Two epidemics of herpangina due to the Coxsackie virus are reported from the poliomyelitis division of the pediatric clinic of the University of Genoa.

In the first epidemic, the initial case was characterized by flaccid paraplegia and meningeal irritation; Coxsackie virus Type A_2 was identified as the causative agent; no poliomyelitis virus could be recovered. About 15 days later, five other cases appeared; these secondary cases had fever, headache, and vesicular eriptions on the soft palate; their illnesses lasted 4 to 12 days. All six patients recovered.

The second epidemic involved 20 patients, the cases appearing over a period of 10 days. These patients were all only mildly sick; each had vesicles on the palate, uvula, and even some on the tonsils; in 13 of the cases Coxsackie virus, Strains A_2 and A_4, was isolated.

Four other and more serious cases with meningoencephalomyelitic symptoms are also reported; they were identified as due to Strains A, A_2, B_2, and B_3. Complete recovery resulted in each case.

The Serum Protein Picture in Children with Tuberculosis, as Determined by Electrophoresis.—In active tuberculosis there is a diminution in the α_2-globulin and an increase in the γ-globulin as determined by electrophoresis. These changes tend to approach normal values as the tuberculous activity diminishes and disappears. Analysis of the serum proteins by the electrophoretic method is believed to be of greater value than the blood sedimentation rate in evaluation of the therapeutic state of the tuberculosis patient.

Oxalosis, a New Metabolic Disease of the Storage Type.—A boy of 11 years was dwarfed and had ichthyosis, a horse-shoe kidney, and marked renal dysfunction. Death followed episodes of acute renal insufficiency with acidosis. At autopsy, histological examinations revealed calcium oxalate crystals in the kidney and in the cartilage of the long bones. A diagnosis of oxalosis was made; this metabolic disease has only recently been identified, the first pediatric case having been described by Vischer (*Schweiz. Ztschr. Path. u. Bact.* 10:286, 1947).

A Case of Methemoglobinemia Due to Aniline.—A 7½-year-old girl developed marked cyanosis, with dyspnea, tachycardia, and drowsiness. The findings proved to be due to methemoglobinemia, caused by a black shoe dye. The treatment was the intravenous administration of 500 mg. of ascorbic acid and oxygen inhalation. The ascorbic acid medication was continued orally.

Some Anatomical Abnormalities of the Gastrointestinal Tract with Vomiting and Malnutrition in Infants.—Clinical and radiological evaluation of infants with vomiting is essential for accurate diagnosis and correct medical and surgical treatment. X-ray pictures of the abdomen of children with many of the congenital defects are shown.

Monatsschrift für Kinderheilkunde, Berlin

104:475-508 (Dec.) 1956

Rickets and Resistance to Infection. W. Theopold, K. E. Sudhoff, and Inge Schulte-Nickell.—p. 475.
Disturbances in Heat Regulation and Endogenous Hypothermia. Guenter Janssen.—p. 478.
The Psychopathology of Brain Damage in the Young Child. Hedwig Wallis.—p. 480.
Typical Electrocardiographic Changes with Tricuspid Atresia. Joachim Stoermer.—p. 484.
* BCG Vaccination in Hessen. Maria Daelen and Harald Saame.—p. 487.
Observations Regarding Marked Increase in Contact Cases of Poliomyelitis. Hans Radl.—p. 494.
Chemistry and Hygiene of Milk. Ernst Mueller.—p. 496.

105:1-40 (Jan.) 1957

The Circulatory Effects of Megaphen and Atosil in Childhood. Guenter Janssen and Hans Guenther Staemmler.—p. 1.
The Trace Element Fluorine and Dental Caries. Heinrich Hornung.—p. 4.
Clinical Studies on the Efficacy of the Second Carbohydrate. T. Brehme and A. Jaeger.—p. 6.
Diagnosis and Treatment of Orthostatic Dysfunction in Children. Trial with the Preparation Carnigen. Kurt Brueck and Dieter Oltmann.—p. 7.
Report of a Poliomyelitis Epidemic in a Nursery. P. Krepler.—p. 13.
Report of an Outbreak of Poliomyelitis in a Pertussis Ward. H. Zischinsky.—p. 14.
Virological Studies Concerning the Etiology of Two Institutional Outbreaks of Poliomyelitis. P. Kraus.—p. 17.
Angiocardiography in the Diagnosis of Obscure Disturbances of the Mediastinum. H. S. Otto and H. Schaefer.—p. 19.
* Treatment of Infantile Dyspepsia, Especially That Due to E. Coli, with Neomycin. F.-W. Wedemeyer.—p. 23.
Aortic Stenosis with Morquio's Disease. W. Thoenes and K. Holldack.—p. 26.
Constitution and Heredity. Joachim Wolff.—p. 29.

105:41-80 (Feb.) 1957

Diagnostic Significance of Uropepsinogen in Childhood. Gustav-Adolf von Harnack and Lore Nahnsen.—p. 41.
Differential Diagnosis and Course of So-Called Coin Lesions in the Lung. Lothat Weingaettner.—p. 43.
Fasciola Hepatica Infestation in Childhood. K. Frank.—p. 46.
* Clinical Course of Hepatitis in 50 Infants. S. Molnar.—p. 49.
Infiltration of the Bile Ducts with Albumen in Premature and Full-Term Infants. Gerhard Veith.—p. 53.
Differential Diagnosis of Neuroblastoma of the Sympathetic Nervous System. Peter Heinz Koecher and Albertus Burmeister.—p. 56.
Etiology and Pathogenesis of Juvenile Kyphosis and Scoliosis. H. Arnold.—p. 61.
BCG Vaccination with Fluid and with Dry Vaccine (Made by Behring Co.). G. Kroll and H. Spiess.—p. 65.
Circulatory Impairment with Fulminating Meningococcic Sepsis. Fritz Graser.—p. 67.
A Case of Omphalitis with Pylephlebitis, Multiple Liver Abscesses, Lung Abscesses and Osteomyelitis Resulting in Complete Recovery. Klaus Betke and Heribert Richarz.—p. 70.
Metabolism and Diseases of Metabolism. Heinz Hungerland.—p. 73.

105:81-120 (March) 1957

Quantitative and Qualitative Cell Values in the Cerebrospinal Fluid of Patients with Nonpurulent Meningitis in Childhood: Diagnostic Significance of Cerebrospinal Fluid Cell Values. O. Lombos, L. Szoeyi, M. L. Radek, and I. Kelemen.—p. 81.
Gastric Digestion of Homogenized Milk in School Children. Eleonore Czech.—p. 88.

Bacterial Dissemination of Retrotympanic Otitis in Infancy. C. Wunderlich.—p. 90.
Clinical Picture of Retrotympanic Otitis in Infancy. C. Wunderlich.—p. 94.
Development and Prognosis of Calcified Pulmonary Conglomerates. H. D. Renovanz.—p. 99.
* Results of Treatment of Hypertrophic Pyloric Stenosis in 460 Nursing Infants Between 1926 and 1956. H. Kehl and R. Lange.—p. 105.
Culture of E. Coli Bacilli Causing Enteritis. K. Hoffmann.—p. 107.
Physiology and Pathology of the Nervous System. H. R. Wiedemann.—p. 108.

BCG Vaccination in Hessen.—In 1953 results of BCG vaccination performed on children living in 23 counties in the state of Hessen in Germany were reported. Among vaccinated 70,224 children and adolescents, 43 developed tuberculosis within a four-year observation period; among 92,145 tuberculin-negative controls there were 319 cases of the disease. This represented a morbidity ratio of 1:5.7. Following two more years, a review of the case material revealed only 18 certain cases of tuberculosis among the BCG-vaccinated group, all with successful vaccination; in 8 further patients diagnosis could not be established with certainty. This changed the morbidity ratio to 1:9.5.

Treatment of Infantile Dyspepsia, Especially That Due to E. Coli with Neomycin. Neomycin was found to be an effective, well-tolerated, and nontoxic drug in the treatment of infantile dyspepsia due to E. coli. Advantages as compared with other antibiotics, especially chlortetracycline, were more rapid onset of formed stools, higher weight gains immediately after onset of therapy, decreased incidence of relapses, and shortened duration of therapy.

In vitro studies showed all types of E. coli to be sensitive to neomycin. Effective dosage ranged from 25 to 50 mg. per kilogram per day, depending on the severity and duration of the illness.

The Clinical Course of Hepatitis in 40 Infants.—Infectious hepatitis was found in the environment of 3 of 50 infants with hepatitis studied in a Hungarian hospital. It was impossible to make a differential diagnosis between infectious and serum hepatitis in view of the fact that techniques were lacking to distinguish the two entities. The three infants with a history of contact with hepatitis developed the first signs of their disease 20 to 30 days afterward. Forty of the infants had received transfusions and/or injections 60 to 120 days prior to onset of their disease. Although in these infants infection by inoculation could not be excluded, it was also possible that they were infected by members of the nursing personnel, two of whom had hepatitis at the onset of this epidemic. No evidence or history of hepatitis could be ascertained in blood donors; they also had normal liver-function tests. In 40 of the infants either inoculation or contact could serve as the etiological factor, whereas in 5 patients neither factor was operative. The mother of one infant had become jaundiced on the day prior to delivery. Despite immediate separation from his mother, this infant became dehydrated and comatose at 4 weeks of age; he developed hepatomegaly and abnormal liver-function tests. Another infant had been wet-nursed by a woman during the incubation phase of hepatitis. The infant developed the disease two months later.

The highest incidence occurred during the spring and fall. Prodromata included fever, anorexia, and gastrointestinal symptoms. Jaundice on admission was found in 49 infants. Nine infants died. Most infants showed decreased weight gain during their illness.

Results of Treatment of Hypertrophic Pyloric Stenosis in 460 Nursing Infants Between 1926 and 1956.—There were 460 nursing infants (349 boys and 111 girls), of whom were breast-fed, who developed hypertrophic pyloric stenosis between 1926 and 1956; 340 underwent pylorotomy by Ramstedt's technique, whereas the remaining 120 were treated conservatively. Of the 460 infants, 17 were premature. Two of the thirteen surgically treated premature infants died. None of the four conservatively treated premature infants died. Conservative treatment consisted of small feedings, gastric lavage, and injections of atropine and phenothiazine. Subcutanous injections of homeopathic doses of nicotinic acid proved effective for pure spasms. Nine patients were admitted for pure spasms. Nine patients were admitted with a diagnosis of pyloric stenosis but had "cascade stomachs" as shown by x-rays.

Postoperative treatment was carried on for from 7 to 10 days, until primary wound healing was completed. The postoperative period was shortened in breast-fed infants; 52 patients were discharged as cured between the 7th and 15th postoperative days; 247, by the 30th day, and 280, by the 50th day. Of the 120 conservatively treated infants, 11 died; 8 of these died of pneumonia acquired in the hospital and 3, of acute nutritional disturbances. Of the 340 children operated on, 19 died. Deaths were due to atrophy, debility, pneumonia, intestinal infections,

circulatory failure, and nutritional disturbances. None of the deaths could be ascribed to the surgical procedure per se.

Radiology, Syracuse, N. Y.

68 (May) 1957

* Roentgenographic Findings in Familial Dysautonomia. Rob H. Kirkpatrick and Conrad M. Riley.—p. 654.
* The Radiographic Features of Severe Idiopathic Hypercalcemia of Infancy. Edward B. Singleton.—p. 721.

69 (July) 1957

Hypaque, a Safe Medium for Pediatric Intravenous Urography. Richard F. McClure.—p. 101.

Roentgenographic Findings in Familial Dysautonomia.—Familial dysautonomia is a clinical entity which manifests itself during the first months of life. It is characterized by dysfunction of the nervous system with particular prominence of autonomic disturbances. Excessive perspiration, drooling, transient erythematous blotching of the skin, intermittent hypertension and postural hypotension, inability to produce tears, and inadequate temperature control are expressions of the abnormal autonomic function. Indifference to pain, hyporeflexia, poor motor coordination, and retarded motor development are other signs of dysfunction of the central nervous system. Other features frequently observed include emotional instability, cyclic vomiting, pulmonary infections, fever of undetermined origin, difficulty in feeding and swallowing, and breath-holding spells in infancy. Mental retardation and convulsions are occasionally present. Of 80 known patients with dysautonomia, all were of Jewish extraction, with 2 exceptions. The familial pattern suggests transmission by a simple recessive gene. There are no significant laboratory findings.

The roentgen findings in 34 cases at Babies Hospital, New York, are summarized. In 19 cases the chest roentgenograms were interpreted as indicating bronchopneumonia; in 7, delayed maturation; in 6, scoliosis, and in 3, fractures. Bronchopneumonia, usually of a chronic nature, is the most important roentgen diagnosis. The commonest picture is one of patchy increased densities in one or both perihilar regions, with extension of the process into one or two lobes. The condition should be considered when a chest roentgenogram is requested because of fever of undetermined origin or recurrent respiratory infections. The change on the roentgenogram may persist after the disappearance of symptoms. The heart, upper gastrointestinal tract, and central nervous system are usually normal roentgenographically.

The Radiographic Features of Severe Idiopathic Hypercalcemia of Infancy.—Idiopathic hypercalcemia, a disorder of calcium metabolism in infants, has been recognized in two forms, one transient and the other chronic and severe. The former is self-limiting, and after a course of several months there are no distinctive roentgen findings. On the other hand, patients with the chronic form have shown signs of physical and mental retardation, hypertension, systolic murmur, fretfulness, hypercalcemia, acidosis, increased plasma proteins, hypercholesteremia, and evidence of osteosclerosis.

While the etiology remains obscure, there apparently is an abnormal sensitivity to vitamin D which results in an excessive absorption of calcium from the gastrointestinal tract, hypercalcemia, renal parenchymal calcification, acidosis, failure to thrive, and death.

In the author's 17-month-old white patient the long bones, as in all previously reported cases, showed increased density of the cortex as well as of the trabecular structures. Roentgenograms showed increased density of the long bones, ribs, and spine. Skull films showed increased density of the cranial vault and base of the skull, with closure of the anterior fontanelle and obliteration of the sagital suture. Alternating bands of increased and decreased density were prominent in the metaphysis. Many conditions are characterized by sclerosis of bone, but none fits the over-all appearance found in idiopathic hypercalcemia. The elevated serum calcium excludes hypoparathyroidism. Chronic renal acidosis may be clinically indistinguishable, but the bone changes are those of rickets or osteomalacia. Engelmann's disease appears at a more advanced age. Fluoride poisoning should be readily excluded by careful history taking and by laboratory findings. Other conditions which should readily be excluded are myelofibrosis and myelosclerosis, vitamin D intoxication, and osteosclerosis, occasionally seen in premature infants.

Rivista di clinica pediatrica, Florence

59 (March) 1957

* Tachycardia, an Early Sign of Measles Infection. G. Baldasseroni, M. Giusti, and S. Mori.—p. 225.
Clinical Statistics on Some Cases of Aseptic Lymphocytic Meningitis. P. Moggi and S. Mori.—p. 240.
* Experimental Data on a Type of Vaccination Using Petragini's Anatuberculin and BCG. F. Ragazzini and C. La Causa.—p. 255.
Antidiphtheritic Vaccination in the Course of Cortisone Treatment in Guinea Pigs. A. Masi, M. Acocella, and M. Acconci.—p. 265.
The Influence of Cortisone on the Development in Vitro of Bacterial Resistence to the Antibiotics (Staphylococcus Aureus). G. Bartolozzi, P. Cocchi, and M. Acocella.—p. 281.
On the Resistence to Antibiotics of Staphylococcus Pyogenes: Study on Strains Obtained from Air in the Hospital and from Patients. M. Acocella, C. Panero, and A. San Giorgi.—p. 298.

Tachycardia, an Early Sign of Measles Infection.—The authors were able to examine a group of children daily following exposure to measles. Twenty-three children developed measles. Twenty-two of these children developed a tachycardia (120 to 140 beats per minute) prior to the appearance of the exanthem; the mean time of the noting of the tachycardia was the 5th day prior to the breaking out of the rash; it was noted as early as the 13th day in one child and in two only 2 days before the rash appeared. In only 21 of the children were Koplik spots detected; these were detected in none of them before the second day before the exanthem. The claim is made that the finding of tachycardia allows of an early diagnosis of measles.

The suggestion is offered that the tachycardia may be due to multiplication of the virus in the myocardial fibers following the viremic stage of the disease.

Experimental Data on a Type of Vaccination Using Petragini's Anatuberculin and BCG.—Guinea pigs were vaccinated first with anatuberculin and five months later with BCG. After another five months, an injection of living Koch's bacilli was given. After 44 days the animals were killed and autopsies were performed. These animals showed much less tuberculous lesions than control animals which had received no vaccine or those which had received injections of only one of the two vaccines, anatuberculin or BCG.

News and Comment

ANNOUNCEMENTS

First Asian Regional Paediatric Congress.—The First Asian Regional Paediatric Congress will be held in Singapore May 26-30, 1958. The regions invited are the Indian Sub-Continent, the Far East, South-East Asia, and Australasia. Any doctor who is interested in attending should write to the Organising Secretary, First Asian Regional Paediatric Congress, Paediatric Unit, General Hospital, Singapore 3.

Oral Examinations of the American Board of Pediatrics in 1958.—The following rules will govern selection of candidates:

1. Candidates must have passed a written examination.

2. Candidates will be called in the order in which their applications were received. Since only a predetermined number can be examined orally in a given year, those enrolled for the written examination who are in excess of that number will be designated as "alternates." They may be called to fill vacancies that develop or may not be called until 1959.

3. Candidates will not be called far in advance of their eligibility date. Therefore, please do not choose a date more than one month prior to the same.

4. Candidates should make a second choice, as the list for each session must be filled. "Alternates" should also list a first and second choice, and, so far as possible, these will be heeded. (Refusal of an appointment will not prejudice subsequent call, but candidates are expected to accept an appointment within two years following passing of the written examination unless an extension is granted by the Board, upon written request by the candidate.)

5. All candidates for oral examination in 1958 should make their choices now. Do not wait to learn the result of your written examination. So far as possible, your choices will be heeded.

Oral examinations in 1958 have been scheduled as follows: (1) Memphis, March 21, 22, 23, 1958; (2) Atlantic City, N. J., May 3, 4, 5, 1958; (3) Cincinnati, June 13, 14, 15, 1958; (4) Chicago, Oct. 24, 25, 26, 1958; (5) New York, Dec. 5, 6, 7, 1958.

Address inquiries to The American Board of Pediatrics, Inc., 6 Cushman Rd., Rosemont, Pa.

Fellowships of the National Foundation for Infantile Paralysis.—The following fellowships and scholarships are offered by the National Foundation for Infantile Paralysis.

Fellowships

Medicine and the Related Biological and Physical Sciences: For scientists who are preparing for careers in research and/or academic medicine. Eligibility requirements include an M.D., Ph.D., or equivalent degree.

Preventive Medicine: To prepare physicians for the teaching of preventive medicine. Eligibility requirements include an M.D. degree; one year internship; two years of training and experience in one of the areas related to preventive medicine.

Rehabilitation: A. For physicians interested in rehabilitation as it relates to their fields of specialization. B. For residents in physical medicine and rehabilitation. Eligibility requirements include an M.D. degree; one year of internship; license to practice medicine in the United States.

Orthopedics: To provide advanced training for surgeons interested in teaching or research in orthopedics. Eligibility requirements include an M.D. degree; one year of internship; completion of requirements for certification by The American Board of Orthopedic Surgery or equivalent training; license to practice medicine in the United States. Age limit is 36.

Physical Therapy Teaching: Eligibility requirements include baccalaureate degree; significant experience as a physical therapist for three years or more.

Occupational Therapy Teaching: Eligibility requirements include baccalaureate degree; significant experience as an occupational therapist for three years or more.

Scholarships

Physical Therapy: To assist students in completing their education in physical therapy. Eligibility requirements include (1) baccalaureate degree, or candidacy for the baccalaureate degree; (2) specified science courses; (3) age limit 36.

Medical Social Work: To assist students in completing their education in medical social work. Eligibility requirements include (1) a baccalaureate degree; (2) completion of one academic year of graduate work education; (3) age limit 38.

For further information write to Division of Professional Education, National Foundation for Infantile Paralysis, 301 E. 42d St., New York 17.

GENERAL NEWS

Rehabilitation Center Dedicated in Stamford.—A rehabilitation center for the physically handicapped, termed one of the most modern facilities of its kind, is being dedicated today in Stamford, Conn. The Center, which will be known as the Rehabilitation Center for the Physically Handicapped, Inc., is operated by a chapter of the Connecticut Society for Crippled Children and Adults, Inc. The Stamford Center, completed at a cost of $475,000, is considered a prototype for rehabilitation units. The Center was designed by Sherwood, Mills, and Smith, architects, of Stamford, noted for their design work in the school and institutional field.

The new building will serve as a center for outpatient treatment and training for persons with physical disabilities. It includes facilities for physical, occupational, speech, and hearing therapy. The completely air-conditioned building also provides facilities for such services as prevocational testing and a school-readiness program for children. A work area also is provided for a part-time chief of medical services and a part-time psychologist.

WHO Committee on International Quarantine.—*Smallpox Brought into Eighteen Countries by International Travellers.*—No less than 18 countries were infected with smallpox by international travellers last year, and as a result eight of them suffered epidemics of this quarantinable disease, according to the World Health Organization Committee on International Quarantine.

At a recent meeting in Geneva the Committee warned against any relaxation of vaccination measures against smallpox and called for the use of potent vaccines as well as correct vaccination procedures. Moreover, the Committee stressed the need for medical and other personnel who come in contact with travellers to maintain a high level of immunity against smallpox by repeated vaccination. In the course of these epidemics, some doctors treating tourists caught the infection and died.

The WHO experts also drew attention to the advantages of dried smallpox vaccine for mass campaigns. Dried vaccine is easily transportable, remains effective without refrigeration, and does not spoil, even in the tropics.

The eight countries where smallpox epidemics took place were Ceylon, Ghana, Iran, Italy, Lebanon, Sierra Leone, Sudan, and United Kingdom. The countries where smallpox was imported without spreading to the population were Argentina, Fed. Republic of Germany, Greece, India, Iraq, Jordan, Netherlands, Paraguay, Syria, and Uruguay.

International Control of Malaria.—The Committee on International Quarantine reviews each year the working of the International Sanitary Regulations, which govern trade and travel by land, sea, and air in some 170 states and territories.

In this connection, the WHO Committee examined the possibility of countries that have successfully eradicated malaria being again reinfected by travellers, but it decided that it was too early to amend the Regulations and officially declare malaria a quarantinable disease.

The Committee suggested that no special antimalaria measures should be imposed on international travellers but that antimalaria drugs could be given to migrants, seasonal workers, pilgrims, and others travelling in large groups as a safeguard against the reintroduction of the disease into freed countries. The Committee also recommended that more stringent measures of deinsectization of ships and aircraft be adopted toward the same end.

Influenza Pandemic.—The Committee noted with appreciation that the vast majority of health administrations had not taken measures against the importation of influenza such as would interfere with world traffic.

Members of Committee.—The following members attended the Committee: Dr. C. B. Spencer, Chairman, formerly Chief, Division of Foreign Quarantine, U. S. Public Health Service, Washington, D. C.; Dr. C. K. Lakshmanan, Vice-Chairman, Director-General of

Health Services of India, New Delhi; Dr. B. M. Clark, Deputy Chief Health Officer for the Union of South Africa, Pretoria, Union of S. A.; Prof. A. El. Halawani, Assistant Under-Secretary of State, Ministry of Public Health of Egypt, Cairo; Dr. L. H. Murray, Medical Officer, Ministry of Health, London, England; Prof. E. G. Nauck, Director of the Tropical Institute, Hamburg, Fed. Republic of Germany; Dr. Stevo Posloncec, Port Health Officer of Rijeka, Yugoslavia; Dr. O. Vargas-Mendez, Director-General of Health, San Jose, Costa Rica.

Lifetime Grants for Drs. J. M. Price and Seymour Cohen.—The American Cancer Society has announced the award of grants for two permanent faculty-level positions in cancer research, the first of their kind. The University of Pennsylvania is to receive $224,000, and $392,296 was allotted to the University of Wisconsin. The positions will be filled by Dr. Seymour Cohen at Pennsylvania and Dr. James M. Price at Wisconsin.

The grants were authorized by the American Cancer Society Board of Directors in a new venture toward research programming. Meffort R. Runyon, American Cancer Society executive vice-president, said, "The awards are a start toward providing an administrative security for the research community. This program was inaugurated following a study of the total cancer research program and is designed to assist institutions of learning to attract and retain the best personnel trained in the cancer research field."

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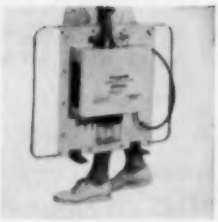

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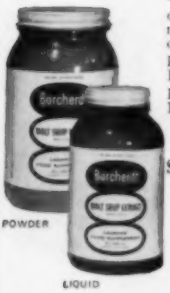

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